

Review

The application of post-market monitoring to novel foods

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Abstract

The role of post-market monitoring (PMM) in the safety assessment of novel foods is critically discussed in order to derive guidelines as to in which situations the application of PMM might be warranted. Available data sources on food consumption and health status, and the methodologies for generating such data are reviewed. The paper suggests improvements to make them more applicable for PMM purposes. It is concluded that any PMM programme must be a hypothesis-driven scientific exercise. PMM can have a role as a complement to, but not as a replacement for, a comprehensive pre-market safety assessment. Its use may be appropriate to confirm that product use is as predicted in the pre-market assessment; to provide reassurance that effects observed in the pre-market assessment occur with no greater frequency or intensity in the post-market phase than anticipated; and to investigate the significance of any adverse effects reported by consumers after market-launch. However PMM is insufficiently powerful to test the hypothesis that any effects seen in the pre-market assessment are absent in the post-market phase. Current methodologies place limitations on what PMM can achieve. PMM should only be used when triggered by or when the focus is on specific evidence-based questions.

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Abbreviations: ADI, acceptable daily intake; BRFS, behavioural risk factor surveillance system; CDC, centers for disease control; DAFNE, Data Food Network; DBPCFC, double blind placebo-controlled food challenge; EAN, European Article Numbering; EDI, estimated daily intake; EFSA, European Food Safety Authority; EPA, environmental protection agency; EU, European Union; FACTS, field accomplishments and compliance tracking system; FAO, Food and Agriculture Organization of the United Nations; FDA, Food and Drug Administration; FFQ, food frequency questionnaire; FSANZ, Food Standards Australia New Zealand; GI, gastrointestinal; GIT, gastrointestinal tract; GM, genetically modified; GMM, genetically modified micro-organism; ILSI, International Life Sciences Institute; JECFA, Joint FAO/WHO Expert Committee on Food Additives; MAFF, Ministry of Agriculture, Fisheries and Food; MRCA, Market Research Corporation of America; NHS, National Health Service; OECD, Organisation for Economic Cooperation and Development; PE, phytosterol-esters; PLM, post-launch monitoring; PMM, post-market monitoring; PME, post-marketing effectiveness; PMS, post-market surveillance; RFID, radiofrequency identity; SCF, Scientific Committee for Food; SuRF, surveillance of risk factors; UK, United Kingdom; US, United States; WHO, World Health Organization.

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Contents

1. Introduction	10
2. Pre-market considerations	11
3. Post-market monitoring – scope and need	12
4. Case studies	14
4.1. Aspartame	14
4.1.1. Pre-market Safety Evaluation of Aspartame	14
4.1.2. Post-market monitoring of intake levels	15
4.1.3. Post-market evaluation of anecdotal reports of adverse health effects	15
4.2. Olestra	15
4.3. Phytosterol-esters	17
4.3.1. Part A (Is the use as predicted/recommended?)	17
4.3.2. Part B (Are the known effects and side-effects as predicted?)	17
4.3.3. Part C (Does the product induce unknown side-effects?)	17
4.4. Starlink maize	18
4.4.1. Background (Uchtmann, 2182)	18
4.4.2. FDA evaluation of consumer complaints linked to foods allegedly containing StarLink maize (FIFRA, SAP, 2201; CDC, 2201)	18
4.5. Conclusions from case studies	20
5. Available methodologies	20
5.1. Food consumption data	20
5.1.1. Food supply data	20
5.1.2. Household data	21
5.1.3. Data on intake by individuals	21
5.2. Health effects	23
5.2.1. Contact centres	23
5.2.2. Disease registers	24
5.2.3. Epidemiological studies	25
5.2.4. Additional sources of health data	26
6. Critical review of methodology and data sources available for PMM	26
7. Conclusions	28
Conflict of interest statement	29
Acknowledgements	30
Appendix. List of participants at the workshop on the application of post-market monitoring to novel foods, 15–17 November 2006, Barcelona, Spain	30
References	30

1. Introduction

The safety of traditional foods and ingredients is generally accepted based on their history of use. The introduction of novel ingredients and the use of novel processes in food production have necessitated the development of approaches to determine their safety. These approaches differ from those that have been used, e.g. in the case of food additives. For novel foods it is not always feasible to achieve high margins of exposure in toxicology studies using levels of administration orders of magnitude above the anticipated intake and a comparative approach has been developed for their safety assessment.

Legislation is in place to ensure that foods placed commercially on the market are safe for the consumer and do

not present an undue risk (e.g. The General Food Law, European Communities, 2002) and specific legislation is in place for novel foods in Europe, Canada and Australia/New Zealand (European Communities, 1997; Canada Gazette, 1999; Australia/New Zealand, 1999). In Europe, novel foods were originally defined as all foods and food ingredients not used for human consumption to a significant degree within the EU prior to May 1997. The EU Scientific Committee on Food grouped them into six classes for safety assessment purposes, ranging from defined chemical substances through complex materials such as plant extracts and macronutrient substitutes, to whole foods from conventional and GM sources. The EU regulatory definition of novel foods has latterly excluded foods and food ingredients produced by, or derived from

genetically modified source organisms since these are now controlled under a separate regulatory regime (European Communities, 1997, as amended, European Communities, 2003). In this document the term “novel food” is used in the broader sense to include foods of genetically modified origin (“GM” foods and crops).

The general principles to be applied in the safety assessment of novel foods have been addressed by the Organisation for Economic Cooperation and Development (OECD, 1993) and the World Health Organization (FAO/WHO, 1996). The fundamental requirement of the legislation is that a rigorous, science-based safety assessment is carried out prior to putting novel foods and ingredients on the market. Wherever possible, a comparative approach is adopted that draws upon analogies with traditional foods having a history of safe use and following detailed analysis and evaluation focuses testing on any critical differences (OECD, 1993; FAO/WHO, 1996; Jonas et al., 1996). In this way, assurance is obtained that novel foods are as safe as the traditional foods with which they are compared.

The concept of post-market monitoring (PMM) has received attention recently as a potential tool in the approaches available for evaluating the safety of novel foods and ingredients. Other terms which have been used to describe the concept of PMM are post-launch monitoring (PLM) and post-market surveillance (PMS). Although there is no mandatory requirement for it in the European Union, PMM was required as a condition for the approval of yellow fat spreads containing added phytosterol-esters (Commission of the European Communities, 2000). Recently, the European Food Safety Authority has recommended that PMM should, where appropriate, be performed for foods derived from genetically modified sources, specifically where there is no traditional comparator available (European Food Safety Authority, 2004a, updated 2006).

The concept of PMM has not been specifically defined but it has been used in the context of testing the conclusions drawn from the pre-market risk assessment, e.g. confirmation of the extent to which the product is being consumed by its target group, and estimation of exposure in other population groups (Commission of the European Communities, 2000). The FSANZ Guidelines suggest that PMM data “will provide additional reassurance regarding long-term safety of products, as well as their impact on the food supply” (Food Standards Australia New Zealand, 2005). In this context, PMM must be seen as a complement to, and not a substitute for, pre-market risk assessment in specific cases. PMM has broader application in marketing, in the assessment of functional efficacy, and in risk management and policy making. While the usefulness of PMM in these applications is acknowledged, they are not within the scope of this document, which is limited solely to a discussion of the role of PMM as a potential complement to pre-market risk assessment as part of the safety evaluation of novel foods. In consequence, any reference in this document to “effect” relates to health effect and

not to any technological or physiological effect that could be considered as “functional”.

The following working definition of PMM is adopted for the purposes of the present discussion:

PMM is a hypothesis-driven, scientific methodology for obtaining information through consumer investigations relevant to the safety of a novel food after market-launch.

Within the context of this definition, this document discusses what activates the need for PMM, when (and when it is not) appropriate to undertake PMM and provides guidance on the methodologies that are suitable and available for the purpose, suggesting where effort needs to be focused in modifying or developing new methodologies that have application to PMM. Although it primarily addresses under what circumstances PMM should be used as a complementary tool in the safety assessment of novel foods, in principle the PMM methodology is applicable to all food groups and not only to novel foods. PMM has been used as a complement to safety assessment in a few specific cases, notably for phytosterol-esters in cholesterol-lowering spreads, aspartame and olestra. These are discussed in detail later in the document as a basis for illustrating the utility of PMM (see Section 4). PMM has not been routinely undertaken to date, nor has it been routinely required.

2. Pre-market considerations

Very few traditional foods or crops that are consumed have been subjected to systematic toxicological and nutritional assessment. Nevertheless, because of their long history and customary preparation and use, they are generally regarded as safe. This is the case even when certain foods, e.g. peanuts, can cause adverse health (allergic) effects in some sensitive individuals and others, e.g. green potatoes, can cause adverse effects in the general population. By acknowledging the importance of customary ways of food preparation, patterns of consumption (including avoidance), and proper storage to limit rot or infestation for example, risks inherently associated with traditional foods are considered acceptable by society.

In contrast, novel foods, novel food ingredients, GM crops (and derived food and feed), genetically modified micro-organisms (GMMs) and, by extension, novel products from the first time use of technologies that have the potential to alter the compositional and nutritional characteristics of traditional foods, each require a detailed pre-market risk assessment. Risk is defined as a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food (Codex Alimentarius Commission, 2005). The first step in an assessment of the risk for human health is thus to identify any hazard that might be posed by a new dietary component, that is the potential of a new food to cause adverse health effects. This is normally carried out through toxicological and nutritional evaluation using *in vitro*, *in vivo* or modelling methods including the use of bioinformatics.

The second step is to characterise any identified hazard(s), qualitatively and quantitatively, often developing dose–response data. The third step has the objective of quantifying intake levels of the particular food or food constituent by consumers (i.e. the exposure). Normally this involves estimating the average and maximum intakes of the novel food and may take into account particular subgroups of the population, e.g. infants, nursing mothers, diabetics, as well as those on subsistence levels of intake or other, non-medically unique populations who may be at-risk due to differences in intake as opposed to biological differences in susceptibility.

Lastly, in the fourth step, the outcome of the hazard characterisation is combined with the intake assessment in order to estimate the risk. This phase of the risk assessment is known as risk characterisation and establishes whether, under the expected conditions of use, any safety issues will arise. Any uncertainties in the risk assessment are identified and the information will then guide requirements for any further assessment to establish safe levels of the new food.

In order to provide the necessary data for a full safety assessment, a typical pre-market testing programme should incorporate the following considerations (Howlett et al., 2003):

- the analytical/compositional and nutritional characteristics of the novel food (including fate in biological systems);
- previous history of human exposure;
- the necessity, appropriateness and outcome of animal studies;
- the expected applications as a novel food and the predicted exposure;
- the necessity, appropriateness and outcome of studies in humans.

The programme should be seen as a coherent whole. Each of these considerations should be assessed for its contribution to the reduction of uncertainties inherent to the others and reassessed as part of an iterative process in which the totality of the information available is taken into account.

3. Post-market monitoring – scope and need

PMM has been described (under the heading PLM) in a previous activity undertaken by ILSI Europe (Howlett et al., 2003). It was described as a means to confirm that the actual intakes of a novel food are within the anticipated range and that there are no unexpected effects when a large population (including the young, elderly and sensitive groups, diseased people and those of a diverse genetic make up) are exposed for potentially long periods of time. It may also serve as a tool for surveillance of the diet to monitor compliance with public health goals or to provide indications of how attainment of public health goals may be

enhanced. Elements of PMM focus on the description and quantification of at-risk groups and target groups, and on the description and quantification of any health effects consequent on dietary behaviour. In furthering public health goals it is important to understand both the potential health gain that can be achieved by the consumption of a novel or GM food, and its safety implications.

PMM may appear superficially to be analogous to the PMS systems in place for medicines but it should be recognised that there are important differences (Howlett et al., 2003). With the possible exception of foods for special medical uses, these differences necessarily mean that PMM is more limited in its precision and ease of operation than the PMS in place for medicines. Access to medicines is carefully controlled through use of prescriptions and availability through pharmacies or hospitals, and patients normally can be precise about what medicine was consumed, the amounts consumed and any alleged side-effects. In contrast, novel foods are widely available without prescription through retail outlets and are consumed in combination with a wide range of other foods, making it difficult to relate cause and effect. Therefore, in terms of monitoring adverse events, the main sources of information in post-market surveillance for medicines are primarily physicians and pharmacists, whereas in PMM for foods it is through direct contact between the consumer and the marketing company by use of, e.g. telephone customer contact centres (see Section 5.2.1).

The possible need for further information to reduce the uncertainties that may be inherent to the conclusions drawn during the pre-market safety assessment of novel foods and ingredients is particularly illustrated by the case of allergenicity (see Box 1).

Box 1 Allergenicity: a hypothesis-driven case for a PMM?

Scientific basis

- Food allergy is an immune mediated adverse reaction which requires interaction between the food component and a genetically pre-disposed individual. The prevalence of food allergy sufferers comprises 2–3.5% of adults and 4–8% of children (European Food Safety Authority, 2004b). Although it affects a limited but apparently increasing proportion of the population, food allergy has important health and socio-economic impacts.
- New protein(s) introduced into the diet, or structurally altered during processing, may have the potential to sensitise pre-disposed individuals or to elicit reactions in already sensitised individuals. There are currently no definitive methods to demonstrate a complete absence of allergenic potential. A pre-market assessment of a novel food is based on a weight of evidence approach to determine the prob-

ability of a new food being allergenic. However, allergic responses are highly variable, depending on genetic diversity, exposure, geographic, socio-economic and environmental conditions, all of which are difficult to mimic in pre-market assessments.

Specific aspects of allergy which impact on the application of PMM

- If the pre-market assessment indicated a high probability for allergic reaction, it is unlikely the food would be approved. Where approval is gained, these products will generally be subject to risk management considerations, such as labelling.
- Adequate traceability and identification of the food in question is required. This may be impossible if an ingredient is present in a wide range of foods.*
- A large enough study population must be used to ensure a statistically valid interpretation, taking into account the low frequency of adverse health effects.* However, allergic individuals constitute targeted sections of the population that may be well identified, organised and informed. They can be motivated to participate actively in a PMM study.
- The collection, validation and recording of case studies must be carefully checked for relevance and veracity by expert bodies (correct clinical diagnosis, link to food consumed, and clinical history).* Models of severe allergic reaction registries and all-ergo–vigilance systems have already been developed in some countries.
- A PMM must be a transparent process, with all relevant stakeholders involved, e.g. food companies, at-risk groups of consumers, physicians (including specific associations and expert networks) and should be evaluated by independent and competent authorities.*

*These aspects are of relevance to PMM in general, not just to PMM for foods with allergenic potential.

PMM may provide the means to evaluate the actual intake of a food by consumers and may increase the probability of detecting adverse effects in small, well characterised segments of the population deemed most at risk in the pre-market assessment, when they are exposed to the food during long periods of time under conditions of every day life. It may thus provide helpful reassurance that the potential for an adverse effect, judged *a priori* during the pre-market assessment to be of low probability, is indeed unlikely for the significant majority of consumers.

This view of PMM as a means to complement but not to replace elements of the pre-market assessment is supported by that of the EFSA Scientific Panel on Genetically Mod-

ified Organisms. In its guidance document (European Food Safety Authority, 2004, updated 2006) the Panel stated that “as pre-market risk assessment studies cannot fully reproduce the diversity of the populations who will consume the marketed product, the possibility remains that unpredicted side-effects may occur in some individuals, such as those with certain disease states, those with particular genetic/physiological characteristics or those who consume the product at high levels”. The Panel noted that risk assessment also relies on an estimate of the intake of the food which is variable and subject to uncertainty before the food is marketed.

PMM is not a routine requirement for the approval for a novel food. Up to now, there have been very few examples of a PMM designed specifically for foods or food ingredients, and very few examples where it has been considered necessary by regulators and required as a condition of approval. However, forms of PMM are often used by industry on a voluntary basis to monitor the performance of new products in the market place. With increasing numbers of novel foods being developed specifically for beneficial health effects, and the introduction of exotic foods into the diet, some kind of PMM may be useful as a means to monitor the effectiveness and nutritional performance of foods post-market. Consideration of the requirement for a PMM for any purpose needs to be assessed on a case-by-case basis. Criteria that may trigger discussions over the requirement for PMM as a complement to the pre-market assessment of safety are as follows:

- If the estimated daily intake (EDI) is close to the acceptable daily intake (ADI): to monitor the real consumption patterns.
- Where an original application was for one product, the exposure to a novel ingredient was limited. Further applications leading to several different products being marketed will have the potential to change the original exposure estimate. This may have consequences for the previously established acceptable margin of exposure which need to be monitored.
- If a product was intended for use in foods for certain target populations it may be desirable to monitor the extent of use by the target population and/or by other groups in the population.
- To monitor potential misuse of a product (over-consumption, or use in applications not originally intended).
- Any food (traditional or novel) may have known potential to exert side-effects. Effects which are severe in nature and are likely to reach a level of significance for health would preclude the marketing of the food, but other effects (e.g. laxation), while observable, may be of lesser health significance. Pre-market assessments address the possibility of these occurring but reassurance that any occurrence in the general population is of low frequency and intensity via PMM would be important.

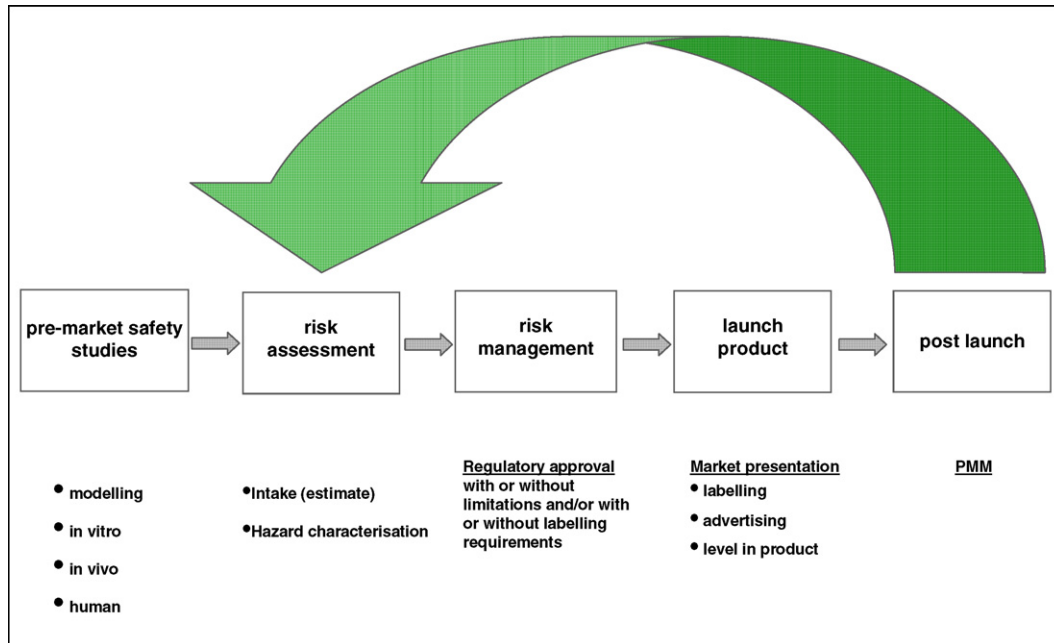


Fig. 1. PMM: a complement to pre-market risk assessment.

- In order for a novel food to be granted approval, the conclusion of the pre-market safety assessment would be that it would not be expected to cause any significant adverse effects once launched. However, if a reasoned hypothesis suggests reassurance of this is required, a system needs to be in place to collect any ‘signals’ which may be suggestive of a health-related event. Such an approach may involve company contact centres to collect and collate any self-reported effects that consumers associate with the product.
- Where contact centres passively identify a significant number of unexpected complaints linked to a particular product (passive monitoring) a more pro-active, targeted PMM may be called for.
- If new issues generate a hypothesis post-launch, then PMM may be appropriate to explore it.

In summary, PMM can be considered as a potential additional tool to complement pre-market risk assessment in certain cases where appropriate triggers indicate a particular need (Fig. 1). PMM should be seen as a response to address specific questions and not as an open-ended activity undertaken as food vigilance.

4. Case studies

The methodology chosen and used for PMM is dependent on the questions asked and the products (or ingredients) surveyed. The need for any PMM is different for each case, and therefore the ‘ideal’ methodology will differ from case to case. Some lessons can be learnt from the following experiences.

4.1. Aspartame

The high-intensity sweetener aspartame (L- α -aspartyl-L-phenylalanine methyl ester) was introduced on the market as a sugar substitute following regulatory approval in the United States more than 30 years ago (Food and Drug Administration (FDA), 1974). It has particular value to diabetics and those on weight-reducing diets. It is regulated not as novel food but as an intense sweetener and was therefore evaluated under assessment schemes in place for food additives which were based on ‘classical’ toxicology methods and testing.

4.1.1. Pre-market Safety Evaluation of Aspartame

Prior to regulatory approval an extensive series of studies was conducted to demonstrate that aspartame was not toxic, carcinogenic, mutagenic or teratogenic, had no effects on reproduction and was safe for general use (reviewed in Kotsonis and Hjelle, 1996). A no-observed-effect level in animal studies of 4000 mg/kg body weight was demonstrated and an acceptable daily intake (ADI) for humans of between 40 and 50 mg/kg body weight was set by various expert bodies and regulatory agencies (e.g. Joint FAO/WHO Expert Committee on Food Additives (JECFA), 1980; Scientific Committee for Food (SCF), 1985).

Before approval, the projected average intake level of aspartame in the US was calculated to be 8.3 mg/kg body weight/day if all the sucrose in an average-sized person’s diet were to be replaced by aspartame and, if all sweetened foods were replaced with aspartame-containing foods, it was calculated that the 99th percentile daily consumption

of aspartame would be 34 mg/kg body weight (Food and Drug Administration Food and Drug Administration (FDA), 1981).

4.1.2. Post-market monitoring of intake levels

Aspartame was approved by the FDA for use in dry applications, viz. tabletop sweetener and gelatines in 1981 followed by approval for use in carbonated soft drinks in 1983. By 1984 about 30% of the US population was estimated to consume aspartame and MRCA Information Services (Northbrook, IL) began monitoring aspartame consumption in the US population (Abrams, 1992; Butchko and Stargel, 2002).

From the MRCA survey the average daily intake for the general population of aspartame consumers at the 90th percentile ranged from 1.6 to 3.0 mg/kg body weight from 1984 to 1992. Intake of aspartame at the 90th percentile even by children aged 2–5 years (maximum in 1992, 5.2 mg/kg body weight/day) and diabetics (maximum in 1991, 3.4 mg/kg body weight/day) was only about 7–10% of the ADI in the US.

Surveys have also been conducted of intakes of aspartame by particular groups and general populations in a number of European countries (Finland, France, Germany, Italy, Netherlands, Norway and the UK) and other countries (Australia, Brazil and Canada). All showed intakes that were well below the respective ADIs. For example in the UK the 97.5th percentile of aspartame consumption in diabetics, who would likely be the most frequent consumers of aspartame products was 10.1 mg/kg body weight/day in 1994, only about 25% of the ADI (MAFF, 1995). The data for individual countries is reviewed in Butchko et al. (2002).

4.1.3. Post-market evaluation of anecdotal reports of adverse health effects

Shortly after the marketing of aspartame in the US a number of anecdotal adverse health effects were reported by consumers who linked them to the consumption of aspartame. As a consequence, the manufacturers of aspartame, the NutraSweet Company, developed a PMM system for aspartame to document and evaluate these anecdotal reports. The FDA requested the centers for disease control (CDC) to evaluate these reports (Butchko and Stargel, 2002). The CDC concluded (CDC, 1984) “Despite great variety overall, the majority of frequently reported symptoms were mild and are symptoms that are common in the general populace” and that the way to address the issues raised was through focused clinical trials.

In a 1995 report the FDA recorded that a total of 7232 consumer reports had been received since marketing. The most common symptom reported was headache (19% of those reported), followed by dizziness (7.5%), mood changes (6.7%), diarrhoea (6.6%) and vomiting 3.4% (Food and Drug Administration, 1995). Seizures and convulsions comprised 3.0% of reported effects and the FDA investigated 251 such cases individually. The FDA concluded that

the reports “did not support the claim that the occurrences of the seizures were linked to consumption of aspartame”. Nevertheless numerous studies on both animals and humans were conducted on the basis of these anecdotal reports to test the possibility that the consumption of aspartame could be responsible for some or all of these ailments. The weight of the evidence from these additional, post-marketing studies further confirmed the results of earlier studies on the safety of aspartame and expanded the safety database on aspartame (Butchko et al., 2002).

The lessons to be learned from this exercise were two-fold: firstly that PMM of aspartame-containing products was effective in confirming that the consumption of aspartame even in high consumers in the US and other countries was below the ADIs set by various regulatory bodies; and secondly that, despite the presence of anecdotal information on adverse health effects, thorough testing in further human and animal studies failed to change the conclusions on safety from the original pre-marketing safety assessment.

4.2. Olestra

Olestra is a non-calorie fat substitute made by esterifying sucrose with fatty acids from edible oil. Olestra is intended for use as a macronutrient and is neither digested nor absorbed. Procter & Gamble, the producer of olestra, petitioned the FDA to approve olestra as a food additive for use in savoury snacks. The FDA review was comprehensive and included consideration of olestra safety for human consumption as well as its occupational and environmental safety. Among the many aspects of nutritional safety considered were an assessment of probable consumption, and the cumulative effect in the diet, taking into account any interactions with other nutritional or pharmacological substances in such a diet.

As olestra is neither digested nor absorbed, the gastrointestinal tract (GIT) is the only organ system that is exposed. Therefore, the pre-market toxicological and clinical evaluations focused on gastrointestinal structure and function, and absorption of nutrients from the gut. The FDA acknowledged that it is impossible to feed the fat substitute to laboratory animals in amounts leading to a 100-fold safety factor as used in studies for food additives. Therefore, olestra was fed to animals at the greatest level possible in the diet without gross interference with the animals' food intake due to excessive dilution of the diet with non-caloric material. This led to testing levels up to 10% by weight of the total diet. FDA animal data concluded that there was no toxic effect when olestra accounted for 10% of the total diet (Prince and Welschenbach, 1998).

Controlled human studies (duration 2–16 weeks, 8–32 g/day olestra) showed that daily consumption of olestra-containing snacks reduced absorption of fat-soluble vitamins and carotenoids and increased the occurrence of gastrointestinal (GI) complaints (Peters et al., 1997). The potential chronic (14 days on average) and acute (single-day)

estimated daily intakes (EDI) were computed from the Market Research Corporation of America (MRCA) Information Service (Des Plaines, IL) for a population of 4741 consumers. This 14-day menu census survey annually collected dietary information on 14 consecutive days from 2000 households, including 5000 individuals, representative of US census statistics and allowing for seasonal fluctuations in intakes. Data from only those individuals who ate savoury snacks on at least one of the 14 days were used ($n = 3820$). The model assumes that 100% of all savoury snacks are replaced by olestra-containing savoury snacks. Values were increased by 10% to achieve conservative estimates, on the basis that intakes of fat-free savoury snacks may be high due to caloric compensation. The mean EDI was 3.1 g/day (range 1.8–4.7; P90 4.1–11.0), and the mean acute EDI was 10.2 g/day (range 5.5–16.5; P90 10.2–24.0). On average, savoury snacks were eaten on four eating occasions in the 14-day period (P90, 10 occasions/14 days) (Webb et al., 1997).

In January of 1996, the FDA granted approval for the use of olestra as a food additive to replace conventional oils and fats used in the preparation of savoury snack foods (Food and Drug Administration, 1996). Based on results from pre-market research the FDA required an interim information label on olestra snack packages informing consumers about potential nutritional and GI effects. Furthermore, the food additive regulation specified that olestra contain compensatory amounts of the fat-soluble vitamins A, D, E and K. At the time of approval in 1996 FDA indicated that it would reconvene a public meeting in 1998 to review the post-market experience with olestra to affirm its safety and to review whether the information label was still necessary. In June of 1998, the FDA reviewed new information about the safety of olestra including several large post-market studies (Food and Drug Administration, 1998). For that purpose, the Food Advisory Committee addressed the following questions (Food and Drug Administration, 2003, p. 46401):

- Based on any new data or information are there significant unanticipated GI effects that can be attributed to olestra and are adverse to health?
- Are there significant adverse effects to health due to olestra interfering with the absorption of fat-soluble vitamins or other lipophilic substances?
- Should the label of olestra-containing products be changed in any way?

The FDA required the conduct of PMM studies to assess the accuracy of the assumptions made regarding the level of consumption and the effects on serum micronutrient concentrations. The PMM program consisted of several studies performed at four sites across the USA. The results have been summarised by Allgood et al. (2001). The intake of olestra by the general population was monitored by cross-sectional population studies (random sampling of participants by telephone number) which were

repeated for several years. Nutritional intakes were estimated using a validated food frequency questionnaire (FFQ), and olestra intakes were assessed using a supplementary questionnaire on savoury snack consumption, with as reference period, 'the past month'. The objectives were to assess the short- and long-term effects of the introduction of olestra on serum concentrations of carotenoids and fat-soluble vitamins in representative samples of the US population and in a cohort of olestra users. Findings at one site reported separately ($n = 478$; Thornquist et al., 2000) that nine months after market introduction, 23% of 933 adults had consumed olestra-containing snacks; 15.5% consumed olestra-containing snacks at least once a month with a mean frequency of three servings per month (corresponding to ca. 1.5 g/day olestra); 12% of olestra consumers had a mean intake of at least 2.0 g/day. No significant associations or consistent trends for decreased serum levels of carotenoids or fat-soluble vitamins associated with olestra consumption were found, although cohort members in the highest category of olestra consumption (2 g/day; $n = 20$) had serum levels of total carotenoids that were 15% lower than at baseline (Thornquist et al., 2000). In the findings at the remaining three sites ($n = 2535$ adults, and $n = 272$ children aged 2–17 years) small but statistically significant reductions were found in serum levels of carotenoids and Vitamin E but, while health outcomes were not assessed in the study, the authors concluded that the magnitude of the reductions was unlikely to have any consequence for health (Neuhouser et al., 2006).

Procter & Gamble set up a passive surveillance system, which collected complaints from consumers using toll-free telephone numbers. No unanticipated or unexpected concerns were raised by the 15,000 health-related calls that were received since the market release of olestra (Allgood et al., 2001). Analysis of the calls revealed that GI symptoms were the events most frequently reported. Several clinical studies were initiated to investigate adverse events reported by consumers via contact centres (Allgood et al., 2001). Re-challenge of 98 consumers previously reporting alleged olestra-associated GI symptoms resulted in the conclusion that subjects were no more likely to report GI problems after eating olestra-containing snacks than after eating full-fat snacks (Zorich et al., 1997, 1998). *Ad libitum* consumption of olestra and placebo crisps on a single occasion in 1092 consumers, randomly assigned the two products ($n = 563$ and $n = 529$, respectively), showed no differences in frequency or severity of GI symptoms between the groups (Cheskin et al., 1998). Finally, in a 6-week consumption study in a population of 3181 frequent crisp eaters no differences in GI symptoms were observed between real olestra crisp users and users of placebo chips labelled to contain olestra (Sandler et al., 1999). Overall, it was concluded that olestra consumption resulted in no meaningful GI effects. GI symptoms were reported 50% more often by people who believed that they had consumed olestra—whether or not they actually had.

This observation suggests that information in media reports and on olestra packages concerning possible GI effects may have prompted consumers to erroneously attribute common GI symptoms to consumption of olestra.

In view of the possible reduction in dietary vitamin K absorption and a consequent potential reduction in the effectiveness of the anticoagulant drug Warfarin, a trial was performed in 36 patients. Consumption of olestra-fortified crisps did not significantly affect coagulation status relative to placebo crisps (Sandler et al., 1999).

The majority of allergy-related calls to the toll-free number did not meet the criteria for considering a reaction to be an allergic one. A trial was performed in subjects reporting allergy-like reactions that did meet these criteria. No subjects experienced an allergic reaction after consuming the olestra-containing crisps or after skin prick testing. It was therefore concluded that olestra is unlikely to have allergenic potential (Burks et al., 2001), a conclusion given support by the fact that olestra is not derived from protein.

Based on the information presented, the FDA reaffirmed its original decision that olestra is safe for use in salted snacks (Food and Drug Administration, 2003, p. 46399). A majority of the Food Advisory Committee had stated that the interim information label required on packages of snack foods made with olestra should be changed or omitted to reduce consumer confusion (Food and Drug Administration, 2003, p. 46384) and the labelling requirement was removed.

4.3. Phytosterol-esters

Phytosterol-esters (PE) have been approved under regulation (EC) No. 258/97 on novel foods and food ingredients as an ingredient for use in vegetable oil spreads. PE enhance the blood cholesterol-lowering activity of the spread, by reducing the absorption of cholesterol from the small intestine. The pre-market safety assessment of toxicological and clinical studies had established that there was a reasonable certainty of no harm resulting from consumption of PE at a recommended intake of 2 g/day. However, a requirement of the European Commission decision was to establish a post-launch monitoring (PLM) programme to accompany the marketing of the product, with questions specifically on how much is consumed and whether the product is being used by the target consumers.

However, Unilever voluntarily developed a PMM scheme for PE which was a more detailed analysis than that requested by the European Commission. The scheme consisted of three components: (A) Is the use as predicted/recommended? (B) Are the known effects and side-effects as predicted? (C) Does the product induce unknown side-effects?

4.3.1. Part A (Is the use as predicted/recommended?)

A standard procedure for most manufacturers is to monitor the introduction of new food products into the market place. In this case, market place surveys were

commissioned to check that consumer usage patterns were consistent with marketing expectations, i.e. to establish which consumers are using the product and to estimate how much they are using. This continuous quantitative method of market research provides data direct from households, which are classified into demographic groups (age of primary shopper, size of household, socio-economic group, presence of children and geographical region), and allows a detailed estimate of intake.

The results of the market research have demonstrated that the product is being bought mainly by the target population (adults aged 45 years and above who have chosen to reduce their blood cholesterol) and is predominantly being used by only one person in each household. Intake of the product is lower than the original assumptions even for regular/established users, with median intakes of the spread being less than 20 g/day (or <1.6 g PE/day) (Lea and Hepburn, 2006).

4.3.2. Part B (Are the known effects and side-effects as predicted?)

The known effects of PE have been consistently demonstrated in a large number of pre-market clinical studies, i.e. a beneficial reduction in serum total and LDL-cholesterol levels (Weststrate and Meijer, 1998; Katan et al., 2003). The only observed unintended effect was a small reduction in the serum levels of the most lipophilic carotenoids (e.g. β -carotene).

A 1-year placebo-controlled human study carried out prior to marketing has confirmed that an intake of 20 g/day of a spread containing PE is not associated with a biologically significant lowering of serum carotenoids (Hendriks et al., 2003). It has also been shown that carotenoid levels can be maintained by incorporating the use of PE-enriched spreads into a healthy diet rich in fruit and vegetables (Noakes et al., 2002). Therefore, it is highly unlikely that current intakes of spreads containing PE will lead to biologically significant reductions in carotenoid intake levels in humans.

These investigations were not considered to be wholly PMM studies as some were conducted prior to marketing.

4.3.3. Part C (Does the product induce unknown side-effects?)

Unilever operating companies have telephone contact centres in place for their products, in which consumer comments and complaints are answered and monitored. The contact centre number is available on all packs and Unilever takes advantage of this well established consumer contact mechanism to collect information on potential consumer reactions. This information is gathered in all countries where Unilever is marketing spreads containing PE. This has enabled the monitoring of health-related calls and detection of any trends in unexpected health effects on a global basis, thereby maximising the potential for identifying possible adverse events.

Information on all health-related calls made to consumer telephone contact centres regarding the use of spreads containing PE has been collected and assessed centrally using a well-defined scheme. Given the extensive exposure to spreads containing PE in Europe, the number of health-related calls was very small (227 of 1673 complaints to the contact centre during the period August 2000–2001 were health related). Complaints including health-related calls were highest during the first few months after introduction to the market, but then slowed considerably despite a significant rise in sales. These reports cover a broad range of self-reported conditions (e.g. gastrointestinal, skin reactions) that were subjected to assessment by health professionals and were judged to be well within the normal occurrence of such conditions in the general population with no clear diet-related patterns emerging. The reports reveal no adverse health effects associated with PE and therefore no cause for concern (Lea and Hepburn, 2006).

In summary, data collected in the market place under “real life” conditions have been helpful to confirm the validity of the initial risk assessment and as a basis to check the assumptions used to derive it. In particular:

- (A) the product is being bought by the target population, but the intakes are lower than the assumptions which were made in the original risk assessment;
- (B) effects are as predicted from the pre-market assessment;
- (C) there is no evidence for the occurrence of adverse health effects providing further support that PE-containing spreads are safe for the intended use.

4.4. Starlink maize

Strictly taken, the term PMM is not applicable for the investigations on StarLink[®] maize described below, because the pre-market human food safety assessment was not completed, the trait was not approved for human food use and, consequently, was not commercialised for this purpose. Nor was there any prospective expert involvement in the design and implementation of the programme to collect and validate what were essentially self-reported cases of alleged adverse reactions. Nevertheless, the StarLink case is mentioned in this document as an example of how the evaluation of consumer complaints collected through a consumer contact centre was done.

4.4.1. Background (Uchtmann, 2002)

StarLink is the trade name for maize hybrids genetically engineered to be herbicide tolerant and insect resistant. To provide insect resistance, a gene from a common soil bacterium, a subspecies of *Bacillus thuringiensis* (“Bt”), was inserted into an approved maize variety genetically engineered to express herbicide tolerance. This new gene causes StarLink maize plants to produce an insecticidal protein

known as Cry9C, a substance toxic to European corn borers and other lepidopteran pests.

Grain harvested from StarLink hybrids were, and continue to be, approved for use in animal feed and for non-food industrial purposes such as the production of ethanol. However, StarLink was not approved for direct human food use in the United States because its Cry9C protein appears to be more stable during food processing and takes longer to digest than its counterpart proteins found in other Bt maize varieties approved for both feed and food uses. Thus, US Environmental Protection Agency (EPA) has classified its potential for allergenicity as medium high. StarLink maize was not approved for consumption in the EU or in any other countries that buy US maize.

Some StarLink maize and non-GM maize material, surrounding the Bt maize fields as a pollen trap to decrease pollen drift from StarLink plants, became co-mingled with large quantities of other maize in the harvesting, transportation, storage and marketing processes. In September 2000, traces of *cry9C* DNA were detected in taco bells, other maize-based food products, and maize export shipments; later the Cry9C protein was also discovered in food products. This resulted in several widely publicised voluntary food recalls initiated by the food industry. Subsequently, the FDA began receiving reports of alleged adverse health effects from consumers who had eaten food products containing maize. Of the 51 individuals who reported adverse health effects, 28 reported symptoms that were deemed to be “compatible” with food allergy symptoms and the remaining 23 did not meet the case definition for allergic reactions: 4 experienced symptoms other than those included in the case definition; 5 had symptoms that did not occur within the established time-frame following consumption of the product; 2 had symptoms that were attributed to a previously diagnosed illness; and 12 had meal companions who also experienced gastrointestinal symptoms, suggesting infectious causes of foodborne illness. In the autumn of 2000, Aventis Crop Science voluntarily agreed to end sales of StarLink seed and voluntarily cancelled its pesticide registration for StarLink’s plant-incorporated protectant. Maize containing the Cry9C protein was then bought up by the company and channelled into non-food uses.

4.4.2. FDA evaluation of consumer complaints linked to foods allegedly containing StarLink maize (FIFRA, SAP, 2001; CDC, 2001)

The evaluation comprises those consumer complaints that were received by the FDA between July 1, 2000 and November 30, 2000. The FDA requested CDC’s assistance in reviewing the complaints, and then, with CDC, launched a collaborative study of the clinical significance of the adverse effects reports. Reports received at a later time were not included in the study. Efforts were made through trade associations to find additional consumer complaints,

but the reports provided presented insufficient data so that that could not be included in the study.

The adverse effect reports were logged into a centralised database (Field Accomplishments and Compliance Tracking System, FACTS). Medical professionals reviewed the forms for the following information: the exact symptoms reported; the time period between eating the food and the onset of symptoms; whether treatment was obtained and, if so, the nature of the treatment; and the course of the illness. Medical officers then assigned a rating of “compatible”, “unlikely” or “unknown” for the likelihood that the reactions were allergic in nature.

A number of different symptoms can raise suspicion that a reaction is allergic in nature. The most common IgE-mediated food hypersensitivity symptoms include urticaria (hives), angioedema (swelling of the throat), rhinitis (runny nose), asthma, gastrointestinal symptoms (vomiting and/or diarrhoea) and even anaphylaxis.

For cases that were consistent with an allergic reaction, (rating result “compatible”), further evaluation was done to determine whether the possible allergic reaction was likely to have been triggered by ingestion of a maize product or by other possible causes and, if consistent with consumption of a maize product, whether the maize product consumed actu-

ally contained any StarLink maize. FDA field personnel collected maize food samples from the consumers who reported adverse effects that were found to be compatible with allergic reactions. Eleven food samples were tested for presence of *cry9C* DNA and Cry9C protein. The *cry9C* DNA was not detectable in 10 of the samples tested. The one positive sample was taken from a grocery store and not a consumer’s actual product. In nine of ten samples tested Cry9C protein was not detected. One result was inconclusive since the level was close to detection limit. Additionally, the blood serum of 18 individuals that self-reported adverse effects was tested for IgE-Antibodies to Cry9C protein that would be most indicative of the potential for an allergic reaction to the pesticidal protein with a newly developed ELISA test. IgE-Antibodies to Cry9C protein were not detected in any of the blood serum samples. One individual who had reported allergic reactions on at least three occasions was subjected to skin-prick testing and to a double-blind, placebo-controlled food challenge (DBPCFC) using certified wild-type maize, certified Starlink maize and lactose placebo. This individual did not respond positively to any of the challenges (Sutton et al., 2003).

The recall of products containing StarLink maize was not instigated as a consequence of the analysis of the

Table 1
Summary of case studies of PMM

	Aspartame	Olestra	Phytosterol-esters	StarLink maize
Reason for PMM	<ul style="list-style-type: none"> – Estimated intake close to ADI – Alleged adverse health effects post-approval 	Confirmation of pre-market assumptions concerning intake and consumer nutritional status (fat-soluble vitamins)	Condition of pre-market approval to confirm predictions concerning intake and target populations	Consumer complaints of adverse health effects
Methodologies employed	<ul style="list-style-type: none"> – Intake assessment by household menu survey – Collection and evaluation of anecdotal reports of adverse effects by independent authority 	<ul style="list-style-type: none"> – Intake assessment in random cross-sectional population study by food frequency questionnaire – Passive monitoring for consumer reports of adverse effects (contact centre) – Serum micronutrient levels measured by cohort study 	<ul style="list-style-type: none"> – Intake and pattern of use assessed by market research (direct survey of households) – Passive monitoring for consumer reports of adverse effects (contact centre) 	<ul style="list-style-type: none"> – Collection and evaluation of consumer reports of adverse effects by independent authority (contact centre) – Retrospective intake assessment in “positive” cases by chemical analysis of food and measurement of biomarkers in subjects
Outcome	<p>Authorities agree:</p> <ul style="list-style-type: none"> – Intake confirmed to be within limits identified as acceptable in pre-market assessment – Safety of aspartame confirmed by additional, targeted studies in humans and animals – Link between aspartame consumption and anecdotally reported adverse effects dismissed 	<p>Authorities agree:</p> <ul style="list-style-type: none"> – Intake and usage pattern confirmed as consistent with pre-market assessment – Expected effects confirmed as within background – Consumer-reported allergic reactions not confirmed on follow-up – Targeted clinical study confirmed absence of effect on anticoagulant medication 	<p>Authorities agree:</p> <ul style="list-style-type: none"> – Pre-market assumptions concerning intake and target group confirmed – No unexpected effects of any significance observed 	<ul style="list-style-type: none"> – No association between putative allergic reactions and exposure to StarLink maize; no confirmation of allergenic potential of Cry9C protein
Conclusion	PMM strategy successful in providing reassurance of safety	PMM strategy successful in providing reassurance of safety	PMM strategy successful in providing reassurance of safety	No PMM strategy applied

reported adverse effects. Rather, it was a response to the co-mingling of GM corn approved solely for animal feed with that destined for human consumption. The passive surveillance program for adverse effect reports resulting from consumption of maize products has continued, as is the case for all pesticidal products in the USA.

Experience with the Starlink maize case has shown that it is almost impossible to trace back the derivatives of a specific GM crop through the whole of the food/feed chain. Furthermore, in relation to the FDA's evaluation of consumer complaints, it has shown that:

- the person answering the consumer contact centre needs to be trained and needs to have a documentation form that is appropriately structured (based on a specific hypothesis resulting from the pre-market safety assessment) to collect general and targeted information from consumers;
- if the information comes in through different contact centres, all parties need to collect the same kind of information and in the same manner by means of the same documentation forms;
- the timeline for collecting information and the intervals for evaluating the data should be defined at the beginning of the exercise;
- the analysis of adverse health effects reported by consumers (the conversion of subjective information to objective data) is critical and must be done by qualified experts (i.e. physicians).

4.5. Conclusions from case studies

The PMM strategies employed and their outcomes are summarised in Table 1. With the exception of the case of StarLink maize, PMM provided reassurance of the absence of product-related adverse effects under conditions of actual use within the limits of the methodologies employed. In the case of StarLink maize, any assessment was confounded by the fact that reported adverse effects and the assessment of exposure were anecdotal; attempts to substantiate the reported effects and the incidence of exposure were reactive and, in the case of exposure, were hindered by the fact that the GM-trait was distributed into the food supply in an indeterminate manner.

5. Available methodologies

A case for the selective use of PMM as a complement to the safety assessment of novel and functional foods has been made previously (Howlett et al., 2003; Schilter et al., 2003). However, the authors did not elaborate on the specific methods that should be put in place to support this. It is difficult to define fully during the pre-market phase what the dietary, lifestyle, environmental and social characteristics of consumers will be, or, by definition, to predict what unexpected components of longer-term health

may be affected by ingestion of a food product. While some knowledge of these parameters is key to the design of any prospective PMM strategy, the successful conduct of PMM ultimately depends on the collection of data that accurately reflect food consumption and any associated health effects in a form relevant to the case under study. The data and methodologies suitable for use in PMM are discussed in this section.

5.1. Food consumption data

Information on food consumption is generally derived from three sources: food supply data; data from household food expenditure/consumption surveys; and results of surveys of individual consumers. Many such data exist and are used across the world to track consumption patterns for food items or nutrient intakes (e.g. Beer-Borst et al., 2000; Dennis et al., 2003; Elliott et al., 2003; Henderson et al., 2002; ONS, 2004; Slater, 1991; Slimani et al., 1999).

Routine data collection and analysis of food use is time consuming and expensive so comprehensive data sets of all three types, although often refreshed on an ongoing basis, are usually historic at the time they become available in the public domain. The direct application of pre-existing data sets for the purposes of PMM is therefore subject to limitations (Amanor-Boadu, 2004; Elliott et al., 2003; Robertson et al., 2004).

PMM methodologies should be hypothesis-driven, utilising approaches appropriate to particular cases. These will determine the type of data needed, with methodologies focussing on the collection of brand-specific information whenever possible. Where ingredients are of interest, companies should be encouraged to provide all available recipe information, ideally linking this to branded products using unique identifiers such as the EAN (European Article Numbering) code system. The EAN code is carried on a wide range of commercial products, including food products, as a barcode, enabling the use of electronic scanning to capture information for use in food consumption surveys (e.g. van Erp-Baart et al., 2006).

5.1.1. Food supply data

Food supply, or disappearance, data are used to calculate the amount of food available for human consumption by tracking the production of, and trade in, agricultural commodities. These data do not measure the quantity of food actually ingested, but record the volume of different products available for consumption (annually and at the national level) by estimating the residuals after exports, industrial uses, seed and feed use, subtracting year-end inventories from total production, beginning inventories and estimated imports. Adjustments are made to ensure distribution system losses are accounted for; however it is not usually possible to adjust for miscellaneous non-food uses and changes in retail and consumer stocks as insufficient data is available for these variables.

These data are used in a number of ways, including to estimate average consumption temporally (Garcia-Closas et al., 2005), to show annual changes in consumption of major food groups, to permit analyses of the effects of economic drivers on, e.g. consumption (McMichael, 2001), and to link with mortality and other health data at a national level (Armstrong and Doll, 1975).

The usefulness of food supply data for PMM is, however, limited because they are unable to (i) define geographic distribution to the local level, that is to describe where available food items are purchased; (ii) relate to consumption at the individual level; (iii) provide an assessment of population nutritional health or (iv) link food consumption to health outcome measures at the level of the individual.

5.1.2. Household data

Household food purchase and/or consumption data are available from a number of sources. In Europe the DATA Food NETWORKING (DAFNE) initiative provides a means of examining trends in food availability and intakes across 16 European countries. The data are stratified by population features (e.g. household composition, educational status, occupation) and collected via nationally representative household budget surveys (Naska et al., 2005). Other sources of data on food purchases by households include commercial market surveys based on consumer panels, which can be used to track purchases over prolonged periods and across different demographic groups and countries (e.g. Taylor Nelson Sofres plc, London UK).

The utility of household food purchase data for PMM has been examined in a study which investigated the feasibility of (i) gaining commercially available food purchase information for use in medium- to long-term surveillance of dietary intakes; (ii) assessing its validity relative to national data; (iii) detecting patterns in food purchases across geographic, socio-economic and temporal groups and (iv) linking information on variations in food purchases to health outcomes (Elliott et al., 2003; Robertson et al., 2004). While the study identified many positive aspects of the data sources, the authors concluded that to address the types of hypotheses posed in PMM, considerable additional data were needed. Purchase information would need to be delineated among household members, additional information on foods eaten outside the home would need to be collected and processing methods utilised would need to be examined. Furthermore, there were limitations to the possibilities for linking household food purchase data with health outcomes.

In some countries the availability of retailer loyalty card information provides an additional source of data with potential for use in PMM. These sources potentially constitute a substantial database, comprising the detailed food purchase records of large numbers of households. On brand level purchasing, within the confines of the particular retail chain, these data are particularly useful in providing fast feedback post-launch. However, as with all

household data sources, they provide limited insight into the totality of a household (or individual's) dietary behaviour, given that they record foods as purchased rather than as consumed and include no information on who within the household consumed these items, or on food waste.

It is not clear whether the limitations of the household approach can be overcome in such a way that a population or distinct target group can be adequately described, or that consumers of particular products can be satisfactorily identified. The application of statistical modelling methods to these databases may make them more accessible for the purposes of PMM, allowing reasonable intake estimates to be derived (FAO/WHO, 2005).

5.1.3. Data on intake by individuals

The ultimate goal for dietary assessment in PMM is to gather accurate information about population intakes. However, the availability of intake data at the level of the individual is critical when relationships between dietary intake and biological parameters or health status are assessed. The availability of data on food intake at the level of the individual together with some methodological aspects of the dietary assessment tools used to quantify individuals' food intakes are discussed below in the context of PMM.

Dietary assessment data collected from individuals are routinely available from cross-sectional population studies (e.g. national food consumption surveys) and ongoing cohort and monitoring studies that include a dietary focus. However, the inherent variability in sample demographics, study methodologies and nutrient-composition databases across studies complicates amalgamation of this information. Routinely applied instruments are frequently unable to identify brand use for example and thus potentially lose nutrient-diversity information as a consequence. Similarly in other epidemiological studies methodologies are not routinely designed to identify brand name use, primarily using food frequency information.

The INTERMAP study, based on a non-computerised 24-h recall methodology, provides brand-specific information on food consumption by 18,720 individuals across China, Japan, the UK and USA (Dennis et al., 2003), although several publications have detailed difficulties experienced in this project (e.g. Schakel et al., 2003; Conway et al., 2004). The first data collected for nutritional surveys in Belgium and Germany using a computerised 24-h recall methodology will become available in the near future. The methodology, recommended by the EFCOSUM group (Brussaard et al., 2002), has also enabled collection of information on brand-specific food use. Data are already available for the Netherlands, although they are not yet brand-specific. Work is underway exploring whether such methodologies can be used to generate data on food consumption by individuals in large scale prospective epidemiological studies.

Where short term intake is of interest, dietary recalls or records are generally employed. The number, selection, and

spacing of the days of intake studied is dependent on the food intake, nutrients or foods of interest, day-to-day variation in intake, seasonal variations and the level of precision required. By increasing the number of non-consecutive measurement days, estimates of usual intakes will generally be more accurate; while for ingredients found in high concentrations in only a few foods, the number of observations needed is greater than for those found in low concentrations in a wide range of foods. In some instances, the number of dietary recalls or records needed to address a question might be very high and considerably exceed the size of existing databases. Also the compliance of participants may be negatively affected if the number of measurement days is high. For effective PMM of ingredients present at high concentrations in only a few foods, the additional use of FFQs might be preferable. FFQs gather retrospective information on food use over a defined time-period, providing valuable information for foods consumed infrequently by a considerable proportion of the population. They can focus specifically on products of interest and can easily be administered to a large sample of the population using, e.g. the internet, although where the internet is used there may be issues about the representativeness of the sample population (Rompelberg et al., 2006). A limitation of FFQs is the consideration of alternating brands, producers or product types within a product category over the time period examined in connection with the ability of subjects to remember and to estimate consumption behaviour over longer periods (Bingham, 1987).

Data collected from individuals on single days give more exact information on the amount and description of the foods consumed, and more accurately reflects intra-individual variability. In order to utilise the advantages of observations made over the short term in the estimation of intakes over the long-term, which are often the desired objective, the application of statistical tools is necessary. Relevant methods have been developed and are undergoing further refinement. For example Nusser et al. (1996) and also Slob and co-workers who have developed a statistical model (STEM) to achieve a distribution of long-term intakes in the population taking into account that the consumption frequency of individual food products may vary within and between individuals (Slob and Bakker, 2004; Slob, 1993). Other statistical estimation procedures that are based on the same objective of eliminating or adjusting for intra-individual variability have been tabulated and described by Hoffmann et al. (2002). The methodology allows the estimation of the habitual dietary intake distribution and, e.g. the derivation of the percentage within a population below or above any given intake cut-off point.

Depending on the questions a particular PMM aims to answer, the exact identification of a product may be required to enable assessment of exact contents, physical appearance, standard supply units, recommended intake information, biologically active forms and target groups in addition to amounts consumed and frequency of use. Traditional food composition databases do not usually

contain this level of detail. As the number of novel foods available increases and existing products are reformulated, maintenance of such detailed food composition databases becomes increasingly laborious. Without compulsory ingredient and nutrient labelling or registration of new food items (unless regulated as novel), this process is further complicated. A future option might be to record food products according to a coding system such as the EAN system. The EAN code is widely in use and is usually provided and accessible on food products as a barcode, enabling use of barcode-read information in food consumption surveys (e.g. van Erp-Baart et al., 2006). However, this information is not yet routinely linked to food composition data and is not available for, e.g. fresh foods or foods eaten out-of-home.

Ideally, dietary assessment data collected from individuals over a random selection of days would automatically be linked with barcode information on foods of interest before being combined and processed using appropriate statistical tools to generate intake records for use in the PMM of product and/or ingredient use. The growing use of radio-frequency identity (RFID) tags, which enable data on brand-specific food product use to be captured electronically, might facilitate that linkage in the near future. While such data might not exist at present, or are not yet easily generated, possible interim compromises include replacing individual food consumption data with household data (see Section 5.2.2), or barcode-linked information with specially designed coding systems utilising brand name information such as that used in the INTERMAP study (Schakel et al., 2003; Dennis et al., 2003; Conway et al., 2004). Such systems are, however, labour intensive, subject to inaccuracies within food labelling information and expensive. Other options to optimise the use of dietary assessment methodologies refer to the internet (Rompelberg et al., 2006).

Looking to the future, PMM might benefit from increasing scientific and public health interest in food-groups and their impact on consumers' health at the level of the individual such that the dietary assessment tools being applied in food consumption surveys will be more directed to intake by individuals than in the past. This might on the one hand increase the opportunities to use existing and, in particular, new data sources for PMM. On the other hand consequent developments in nutrition science might result in new or updated dietary assessment tools that are particularly suitable for PMM. Defining the principal requirements of an assessment of food product use with respect to the type of information needed would allow the appropriateness of existing methods and data sources to be evaluated. It may also allow new sources of information which have been overlooked in the past for use in PMM to be identified.

In the case of exposure to an ingredient through multiple products and/or producers, and in other cases when subjects cannot easily identify all the foods which contribute, the identification and use of easily accessible biomark-

ers of exposure should be considered in place of collecting food-use information from subjects through dietary recall or FFQs. This field is rapidly advancing through the development of high throughput techniques that can process considerable numbers of biological samples within a short time period for markers of interest.

5.2. Health effects

Ideally, PMM systems would be sufficiently sensitive to track or identify any potentially food-related health effects. This requires access to sources of information on a range of health status indicators (for conditions from minor gastrointestinal complaints to serious disease) in a form that can be linked to information on food intake. Health surveillance systems exist as ongoing, systematic collections of public health data which are used to inform public health actions, develop health policies, plan and evaluate health promotion programmes and to formulate hypotheses for research (Andersen et al., 2004). In support of specific PMM projects, existing data sources must be better utilised, with companies establishing improved lines of communication through which consumers may report information about possible product-related health effects. The use of companies' customer contact centres and the utility for PMM of health information currently collected for disease registers, population health surveys and epidemiological trials is considered here. The potential offered by some additional, recently emergent sources of data is also briefly discussed.

5.2.1. Contact centres

Contact centres are established by food companies primarily as channels for consumer relations, interacting with consumers via telephone, mail, e-mail and face-to-face. They have two main functions. One is to build consumer loyalty by responding to their queries and concerns; the other is to collate useful information from consumer contacts and deliver it to the departments in the company that are responsible for selling, improving and ensuring the safety of products. This is usually done by recording and stocking (often in the form of a database) detailed information about each consumer and each contact. Depending on the sophistication of the system, contacts may be classified according to a standardised system or captured through the consumer's words. Statistics are tracked and information is summarised and reported according to specific procedures of the contact centre. Consumer contacts with these centres often trigger a response from manufacturers, e.g. to recall contaminated products and could have similar utility as a point of contact for PMM.

Consumers are concerned about what they eat and they may contact food companies or local authorities directly when they have questions about food quality or safety. After analysis of consumer contacts, trends may be visible – e.g. an unusual number of queries may relate to a particular subject, or a certain type of inquiry may occur more

frequently. By providing such signals, contact centres can serve as early warning systems for possible product problems.

Contact centres can be pro-active as well as reactive. In addition to regular tracking, they can make targeted inquiries; e.g. every consumer who contacts the centre can be asked to participate in an online survey about a specific topic. Thus, contact centres are well placed to aid PMM with detecting problems after a product launch. They can provide the first alert of an acute and severe health effect such as food poisoning or allergy. They can also track consumers' reaction to a new product, including consumption patterns.

When a novel food product is launched, a contact centre needs the following resources so it can respond effectively to consumers while at the same time providing feedback to the company:

- information on the new novel food product, such as background, description, specifications, possible questions and answers, possible problems with the product;
- specific training related to the novel product for people who are in contact with the consumers;
- resources to allow issue/media monitoring.

The contact centre staff must be trained to ask open questions to elicit as much information as possible from the callers in an unbiased manner. In order, in particular, to understand the customer's reason for calling and capture their experiences in terms of (i) the use of the product, (ii) the nature of the adverse effects and (iii) their relationship in time. The data need to be assessed for the likelihood of a causal relationship existing between the consumption of the food product and the reported systems. This assessment should be conducted by appropriately qualified individuals, e.g. clinician and/or toxicologist. An example of such a scheme is illustrated in Fig. 2.

There are some inherent limitations to the information that contact centres can provide. In particular:

- they are only effective at gathering information on specific food products;
- the likelihood that a consumer will contact a company is variable, dependent, e.g. on the consumer's culture, country of origin and motivation for the call;
- long-term effects may not be detected because there may be confounding factors or, where effects appear after an elapsed period of time, it is unrealistic to expect the consumer to be able to associate symptoms with consumption of a particular food;
- self-reported symptoms are imprecise indicators of the scope and gravity of a health problem. Self-reported symptoms may be subject to a high number of false positives (e.g. it has been suggested that the incidence of perceived food allergies is probably about 10 times greater than that of actual occurrence, Canadian Biotechnology Advisory Committee, 2002);

- the quality of the information depends on the contact centre’s people and technology (e.g. contact classification, data analysis capacity, possibility to capture and analyse consumers’ verbatim comments). Contact centres have usually initially been created to deal with quality issues or extrinsic safety problems (product contaminations); they are not intended to deal with the intrinsic safety of novel foods or ingredients. Therefore, specific training for this purpose is required for contact centre personnel;
- establishing the causal nature of a link between effects and the consumption of a specific product will be difficult, especially when the quality of the information is poor.

Nevertheless, contact centres can be an important element of a PMM strategy, performing a surveillance function with respect both to food consumption patterns and to the detection and follow-up of adverse effects.

5.2.2. Disease registers

Physician or laboratory reports on new cases of diseases, treatment effectiveness and patient satisfaction indicators are examples of the types of data stored in disease registers. Information contained in disease registers is currently used in three main ways:

1. *Patient care*: Information is used locally or nationally (dependent on registers’ scope) to review care strategies,

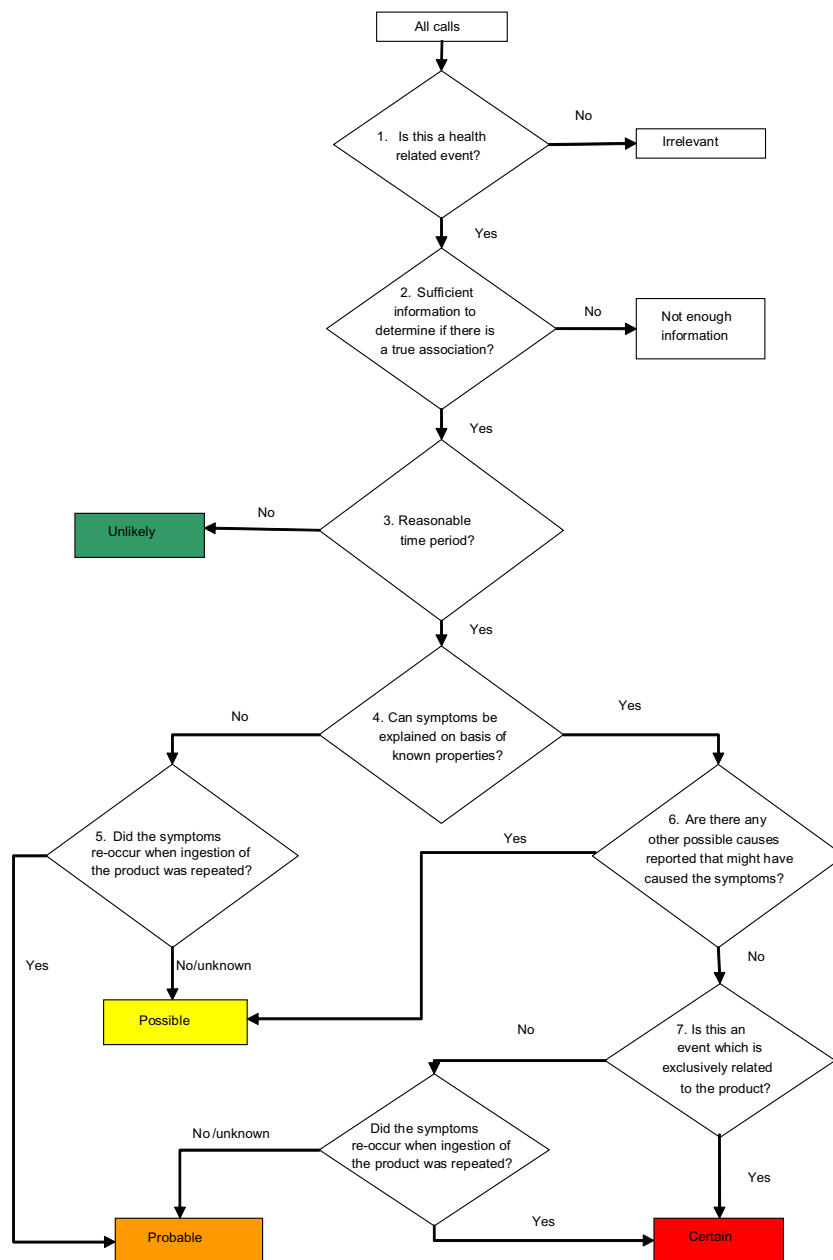


Fig. 2. Consumer response categorisation scheme.

improve monitoring and management of high risk groups, manage demand for health care systems and regulate access to such.

2. *Public health*: Collected data are used to plan the provision of health care for affected (and potentially affected) groups, to monitor the burden of ill health associated with particular diseases in the population, and the impact of preventive measures.
3. *Technology assessment*: The utility of data collected is evaluated using various research tools.

The utility of disease register data for surveillance of the health effects associated with dietary intakes is less robust than demographic, socio-economic or environmental data routinely used by Public Health Observatories and academics to assess the effects of environmental exposure data on health outcomes at the small area level (e.g. www.sahsu.org, accessed 17th July 2006). As discussed previously, one aim of PMM is to determine whether ingestion of specific food items is associated with unexpected health outcomes. Much can therefore be learnt from existing spatial epidemiological techniques utilising disease register-type data and routine health statistics. However, multicollinearity in dietary variables complicates any assessment of intake relative to health outcomes. In addition, dietetic links with health outcomes are not consistent across population groups or levels of exposure. To facilitate such a surveillance system therefore, data collection would be required on a variety of health and lifestyle behaviours in a sample representative of the general population. This level of information is not yet routinely collected. In addition, this dynamic information source requires regular reappraisal to achieve completeness and data quality, while heterogeneity remains evident in every aspect (size, quality, purpose, topic, cost, funding source, etc.). Integrating all register-held data using a common computer language and unique person identifiers might allow collation of information on several important health outcomes while preventing possible double entry of data; however the resulting population sample would constitute only individuals with diagnosed diseases, and therefore would be inappropriately biased for population-wide health surveillance.

Instituting electronic patient records would facilitate amalgamation of general practitioner, hospital and other health records and increase the potential scope for use in more general health surveillance. Such a system would first however require (among other things) ethical and data protection approval before its utility in a wider PMM context for the linkage of disease patterns with specific dietary intakes could be fully realised. Such data could comprise an excellent resource for assessing intake-associated health effects in specific ‘at-risk’ population groups.

5.2.3. Epidemiological studies

Epidemiological studies that relate dietary and other subject-specific or environmental data and host factors with disease risk, taking the individual with his or her char-

acteristics as the analytical unit, comprise perhaps the most suitable study design format for use in PMM. Prospective cohort studies follow the flow of exposures and disease risk in a logical manner. Studies implementing defined, active manipulations of intake or behaviour comprise intervention studies, while observation studies simply monitor usual dietary practices and consequent health status or behaviours. Population-based epidemiological study design methods are used for health surveillance globally.

The World Health Organization (WHO) compiles data on risk factors for chronic disease from each of its member countries. The SuRF 2 (surveillance of risk factors) report makes available the latest health statistics essential for planning and implementing health policy (WHO Global InfoBase Team, 2005). The status of country-level, chronic, non-communicable, disease risk factors and their contribution to the burden of chronic disease in populations are described both spatially and temporally. Standardised questions and protocols are in place to guide information collection across participating countries. However, these are not yet routinely applied, nor do all states or countries yet provide the same information. Therefore, some standardisation procedures are required to for example, homogenize age groups used and definitions applied for overweight and obesity. Central to PMM for potentially food-related health effects, it should be noted that in only 4/46 African, 6/15 Eastern Mediterranean, 23/52 European, 8/35 American, 4/12 South East Asian and 8/27 Western Pacific regions who have provided data used in the SuRF reports, has any dietary information been recorded (28.3% of all regions). The volume of detail provided in this area is variable.

The behavioural risk factor surveillance system (BRFSS) in the United States comprises the largest population-wide health surveillance structure in place in the world. Initiated by the centres for disease control (CDC) in 1984, the BRFSS was designed to empower states and local agencies to target disease prevalence locally by identifying at risk populations and effective health promotion tools, and encouraging their use to help reach national health goals. Using a continuous telephone survey methodology, risk behaviours identified as related to chronic disease, injury and death are monitored across the US. Since 1997, all US states, the District of Columbia and Puerto Rico have routinely collected BRFSS data. A random sampling methodology is used to recruit individuals aged 18 years and older and standardised questions are asked, focused to health behaviours related to leading causes of death and disease. Additional questions are added in specific states where specific areas of concern are identified (e.g. to assess the psychological impact of the Oklahoma bombings). Collected data are analysed by the CDC and other national bodies, identifying necessary amendments to health promotion campaigns across states and increasing media coverage of findings to promote positive behaviour changes for example (<http://www.cdc.gov/brfss/>, accessed 9th November 2005).

As with disease register data however, population surveys tend to investigate risk factors specific to conditions, diseases or at-risk groups. Without availability of detailed and comprehensive health behaviour and dietetic information for a population-representative sample, the utility of the data collected for population surveys, such as those currently in place in Europe, is not yet ideal for use in PMM. Large scale epidemiological studies are hindered by a lack of useable data collection methods for longitudinal assessments of health status and/or detailed (and accurate) dietary intakes, particularly in population samples adequately sized to accurately detect associations. However, if such studies were to apply more detailed and quantitative dietary assessment instruments, or were targeted by specific PMM questions, prospective studies would become a useful means to conduct PMM.

Case control studies can be considered less resource-intensive alternatives to prospective studies. They investigate subjects with a specific disease or health impairment in relation to their previous dietary intake or other characteristics and compare their responses with controls. This design can be useful in PMM because the choice of disease and specific dietary intake can be tailored to address the PMM questions. However, its retrospective nature and susceptibility to selection bias otherwise diminish the usefulness of this design in PMM.

5.2.4. Additional sources of health data

Advances in computer science have generated additional sources of health-data which are currently under-utilised in science. Health authorities, professionals and patients alike can benefit from the use of e-Health facilities. Internet-based applications are extended via health information networks, electronic health records, telemedicine services (e.g. NHS direct), personal wearable and portable devices (e.g. accelerometers), health portals and other information and communication technology-based tools assisting prevention, diagnosis, treatment, health monitoring, and lifestyle management (Commission of the European Communities, 2004). However, the intricate level of data available via such devices as, e.g. downloadable blood glucose meters used by diabetic patients, are seldom used to their full potential. Amalgamation of these data could potentially be of great benefit to PMM systems.

6. Critical review of methodology and data sources available for PMM

The attempts so far made to determine how feasible PMM is for novel foods (Amanor-Boadu, 2004; Wal et al., 2003; Robertson et al., 2004; Elliott et al., 2003; Hlywka et al., 2003), have provided useful insight into what a PMM system should incorporate and what it can realistically expect to achieve.

It is evident from this brief review of the information sources currently available however, that while PMM has to use pre-existing databases as a starting point, there are a number of problems to be solved including sampling bias, insufficiency of resolving power, insufficient exposure-response data, imprecise descriptions of outcomes and inadequate information to estimate the contribution of risk factors to disease development.

At the simplest level, surveillance of the use of a novel food is only possible if the food can be identified and its use in the food chain, as an ingredient in food manufacture or as a food in its own right, can be traced. This is most easily achievable if the food takes the form of an individual branded product or a complete but specific group of products, a food for special medical purposes or a dietary supplement with a targeted population and/or a specific dietary or technological use. In such cases, responsibility for the PMM can most easily be undertaken by food manufacturers. Where monitoring beyond the level of specific food products is concerned, e.g. in cases where the PMM has a broad, ingredient focus, governmental involvement will be justified.

For a new food ingredient, methods must be available to characterise and quantify the ingredient in the complete range of different food products in which it may be found. If data on food consumption is to be gathered through some form of consumer response, consumers must be able to identify the products containing the ingredient and the foods must therefore be adequately labelled to enable this. Absence of traceability precludes the effective implementation of any PMM.

Better estimates of out-of-home consumption are desirable. The on-going development of food product traceability techniques with the capacity for automated electronic data capture in retail outlets using, for example radiofrequency identity (RFID) tags, may offer some prospect of help in this respect. More specific information on individual consumption out-of-home may be available from institutional canteens/restaurants (e.g. schools, hospitals, etc.). In general, consideration needs to be given to the quality of the assumptions necessary to convert data on food availability into intake by individuals (e.g. household v individual, wastage, out-of-home). Attention should be paid to the currency of the data (i.e. how recently the data were obtained), which is of particular importance for composite foods comprising ingredients that may change over time.

The European Commission is funding a project within Framework 6, EUROFIR, to develop a European food composition database. The utility of such a database will depend critically on the availability of recipe data (i.e. information down to the level of individual ingredients) and brand-specific information. Such databases, together with food consumption databases, can provide useful background and reference data for PMM.

To be fully comprehensive for the purposes of PMM, a surveillance system should monitor and evaluate trends in

the use of novel foods where deemed necessary and relate them to health outcomes. This requires systematic monitoring and analysis of intake behaviours, and an assessment of changes in those behaviours made in response to social and environmental influences.

In this light, advanced statistical approaches are of interest. For example, it is important that a methodology be developed to simulate the population distribution of intakes of novel food components in order that the consequences of different future intake scenarios (realistic, trends towards the future and worst case) can be predicted. The simulated distributions could provide information about parts of the population having optimal, insufficient, or excessive intakes. Until now, no general methodology has been developed for this (Kloosterman et al., *in press*). Two approaches are available: deterministic and probabilistic. In the deterministic approach, a single, best guess point estimate of each input parameter (e.g. worst case of consumption and concentration data) is used. The probabilistic approach uses probability distributions for the most important parameters. This latter approach gives insight into the variability of intakes in the population. Special software is needed for these types of calculations. An example has been presented in a report compiled by Willems et al. (2006). Kloosterman et al. (*in press*) have also presented a general method for simulating the intake of food ingredients in a consistent way that allows comparison of results, even though case-specific adaptations and assumptions always remain necessary. Even with incomplete data or data from different sources, habitual intake distributions can be estimated using assumptions, statistical procedures and probabilistic modelling approaches.

As a further stage, health benefits and also health risks can be modelled on the basis of the calculated intake distributions. This is performed in several steps. The first step includes the identification of the health effects in the corresponding populations. Secondly, an exposure-response relationship is identified. And lastly, the information from the intake distributions is combined with the outputs of the first and second steps. This may be applied in a probabilistic manner. The outcome characterises the health impact of a novel food (Hoekstra et al., *submitted for publication*). Several EU-funded initiatives have recently been started with this objective in mind: Qalibra (www.qalibra.eu); BENERIS (www.beneris.eu); and BRAFO (co-ordinated by ILSI Europe). Simulation of effects pre-launch could be of value in designing a PMM study, e.g. in determining the power necessary to test the underlying hypothesis or in identifying specific target groups.

Sophisticated statistical and simulation techniques are also in use in other areas of population-based research and may be applicable, after adaptation, to PMM. However, before such methods are adopted or developed for PMM, the effort required should be justified by consideration of the likely added value that they would

provide. Such techniques may be more readily applicable to exposure data than to adverse effects data. Areas that could benefit from the development of statistical and simulation techniques include signal detection (once data are filtered for quality), analysis of sparse and missing data sets, simulation and sensitivity analysis/scenario modelling, linked exposure-outcome/effect models (although data quality in a PMM study may not be adequate for this purpose), aggregate exposure assessment and dose–response modelling based on pre-market safety data.

Only by addressing all these factors, with the assistance of simulation and modelling techniques as necessary, could the design of a fully comprehensive PMM study be outlined. Achievement of these objectives would require further investment in, among others, national food consumption surveys with particular focus on:

- assurance of continuity in data collection and reporting;
- use of data collection methodologies which better reflect habitual intakes (e.g. a combination of focused FFQs with multiple dietary recalls);
- further development of statistical techniques enabling transformation of reported intakes to usual intakes;
- further investment in food composition databases to retrieve brand-specific information, e.g. based on EAN codes;
- linkage of national food consumption data to transnational databases to enhance the resolving power of data collected locally;
- further data collection on specific dose–response relationships for effects in humans. Such relationships are often only available from animal studies;
- further research on early markers of health effects (e.g. exploration and validation of suitable biomarkers or other measures of intermediate endpoints).

Omics techniques may be of value as probes in identifying biological responses to dietary stimuli. However, for reasons of practical limitation it is not envisaged that these techniques could form an integral part of PMM. Rather, they may have application in helping to formulate and test hypotheses in subsets of individuals and in the development of biomarkers which may then be used as surrogates for health endpoints in larger studies.

While the use of biomarkers in focused clinical trials provides a means of testing specific hypotheses in small target populations, systems providing for the linkage of data on health and nutrition status would improve the resolving power of data collected in cohort and monitoring studies.

Surveillance systems have the advantage of being substantial, but the information that can be retrieved is on an aggregated level. Linkage of data from cohort studies to surveillance systems could provide an opportunity to derive conclusions more relevant at the level of the individual but data sources are currently often difficult to

link together for ethical, proprietary and practical reasons. In developing capacity to undertake PMM, efforts should be made to reduce these difficulties to the extent possible.

Finally, the availability of information on the underlying prevalence of the health effects of concern, in comparable populations, would be very useful in analysing the significance of PMM data.

While the development of all the above tools and data sources is desirable and needs to be pursued, it should be borne in mind that the use of customer contact centres already provides a direct interface between the suppliers of novel foods and consumers. Although at present proprietary in nature, variably operated and subject to their own forms of limitation, these surveillance systems nevertheless deliver information linking the consumption of specific food products to effects in the consumers who use them. Exploration of their potential for further development to reduce their susceptibility to bias through self-reporting and passive capture, improve their transparency through accessibility to independent oversight and introduce cross-industry standardisation may offer an interesting prospect in the short-term for a tool suited for use in PMM.

7. Conclusions

PMM may serve as a complement to the pre-market safety assessment which is undertaken prior to the launch of specific novel foods and ingredients, in which case it is undertaken to meet defined, hypothesis-driven objectives and is solely related to safety aspects. It may also serve as a tool for surveillance of the diet to monitor compliance with public health goals or to provide indications of how attainment of public health goals may be enhanced, in which case it is speculative in nature.

Broadly similar considerations apply to post-market studies undertaken to establish the effectiveness of functional foods, where similar datasets and techniques will also be used. However, the objectives of such studies and the motivation for undertaking them are different from those described here for PMM undertaken in relation to the safety assessment of novel foods. In the interest of maintaining clarity of purpose, it may be helpful to formalise a separate, parallel system for the establishment of “post-marketing effectiveness” (PME) to be followed where the effectiveness of functional foods is the issue to be addressed.

In relation to its role as a complement to pre-market safety assessment of novel foods, PMM may be appropriate:

- to confirm that product use is as predicted/recommended, to relate exposure in use to EDI;
- to provide reassurance that any effects observed during pre-market evaluation occur post-market with no greater frequency or intensity than anticipated;

- to investigate the validity of customer reports of adverse effects which may arise after launch and which were not indicated by the rigorous pre-market assessment, provided there is an adequate system to allow reports to be made and that a suitable hypothesis can be generated.

PMM is NOT appropriate:

- as a tool to replace any steps in the pre-market safety assessment process. Safety should be assured before market-launch;
- to test the hypothesis that any effects identified in pre-market studies are absent in the post-market situation, as it is not possible to prove a negative. The outcome of any such attempt would be limited by the power and nature of the study possible under PMM (e.g. duration of exposure). However, PMM can provide a measure of the confidence that effects will not occur.

Available methodologies and datasets place limitations on what PMM can achieve. PMM undertaken to support pre-market safety assessments of novel foods and ingredients must be focused on specific questions if it is to meet the expectations placed upon it. The objectives of any particular PMM project and the circumstances under which it is to be undertaken will determine the optimum choice of methodology and data source to be used.

The flows of information by which the necessary data are gathered involve a number of different stakeholders who could interact in the PMM programme. In any one programme the stakeholders potentially comprise: the food manufacturer, who may be responsible for the general organisation of the PMM; the consumers and/or consumer organisations; the health professionals, who may also be organized in networks; and an independent expert body, which may often be the appropriate regulatory and/or competent authority. The PMM process should be transparent, with the appropriate connections in place to ensure good communication between the stakeholders.

Before embarking on a PMM study, an appropriate strategy should be developed depending on the purpose of the monitoring scheme. However, there are certain prerequisites which must be fulfilled if any PMM study is to be feasible and provide meaningful results:

- it must be hypothesis-driven (what is the identified concern and what is the hypothesis which links it to consumption of the novel food in question);
- the power of the methodology employed must be sufficient to meet the objectives of the PMM;
- the study parameters must be clearly defined (what is the outcome to be observed, how is it to be measured, what is the timeline involved, who will be involved);
- there must be adequate traceability and identification of the novel food in question;

- there must be reliable assessment of food intake (careful choice of method to use, appropriate to the circumstances of the study);
- the study population must be large enough to ensure a statistically valid interpretation taking into account the likely low prevalence of adverse health effect(s) and the population characteristics (social, geographic, cultural, etc.);
- the collection, validation and recording of case studies must be carefully checked for relevance and veracity by appropriately expert investigators to ensure, e.g. correct clinical diagnosis, a link to the food consumed and subjects' clinical history. Health effects should be characterised by codification in accordance with an internationally recognised system, e.g. the WHO International Classification of Diseases (ICD)-9;
- a good PMM should be conducted through a transparent process fully involving all relevant stakeholders.

Where consumer contact centres are used, operators must be carefully trained to collect general and targeted (based on the specific hypothesis dictating the need to perform a PMM) information from consumers. Even then,

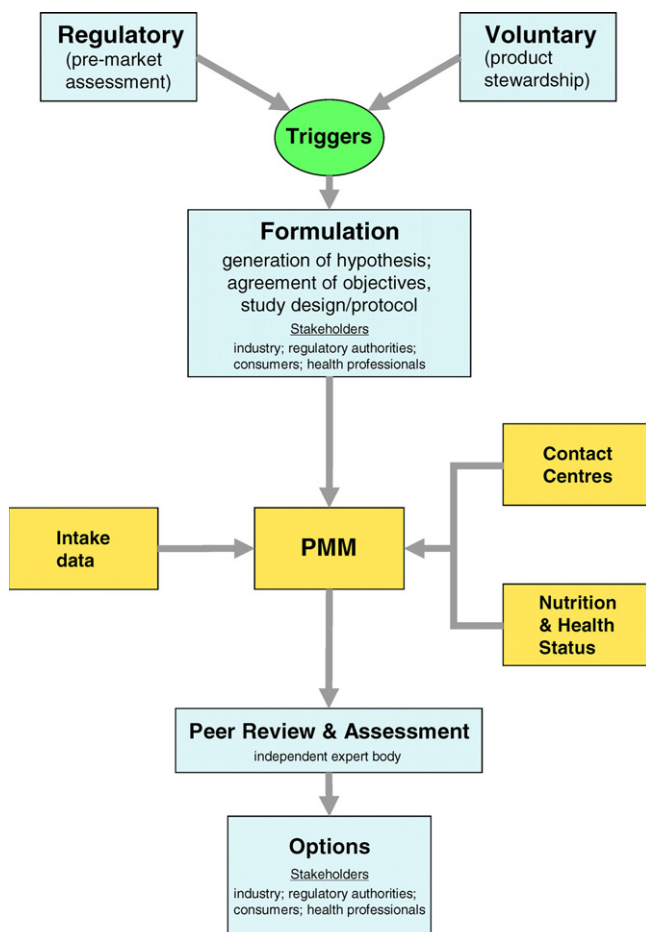


Fig. 3. Strategy for a hypothesis-driven PMM on a novel food.

the difficulty of linking any effects reported to the consumption of particular food products should not be underestimated. While contact centres can provide signals which suggest that effects may be occurring, establishment of causality will always require follow up and more focused studies.

In order to take these considerations fully into account, the design of a PMM study must necessarily be determined on a case by case basis to meet the demands of any particular novel food and the questions prompting the need for monitoring. Such questions may arise during pre-market evaluation or post-launch, e.g. as a result of consumer feedback.

The various potential objectives of a PMM are, in general, independent of each other. A PMM may be conducted to address just one of the objectives, and where more than one is addressed, these may often be undertaken as separate activities. The methodology and the requirements for data and data-linkage will depend on the focus of any particular activity. Although linkage between exposure and effects data will be a requirement in some cases, it may not be essential to the achievement of the objectives of others.

The outcome of a PMM may give rise to the need for additional studies, such as more specific, focused studies, e.g. a placebo-controlled clinical trial. At the other extreme, long-term epidemiological studies may be indicated. There is a hierarchy of study designs, each of which may have different power and confidence levels.

A strategy for the initiation, co-ordination and conduct of a PMM is proposed in Fig. 3.

Conflict of interest statement

Hepburn P.: Employee of Unilever a FMCG company which also develops and markets novel foods including those containing phytosterol-esters.

Howlett J.: Received an honorarium from ILSI Europe for his contribution to the drafting of the paper and for acting as a rapporteur at the Workshop at which the paper served as principal discussion document.

Boeing H.: None.

Cockburn A.: None.

Constable A.: Employee of Nestlé.

Davi A.: Employee of Groupe Danone, a food company which innovations involve the use of novel foods and novel ingredients.

de Jong N.: None.

Moseley B.: None.

Oberdörfer R.: Employee of Bayer CropScience AG, a company involved in R&D and Marketing of genetically modified plant crops.

Robertson C.: None.

Wal JM.: None.

Samuels F.: Employee of ILSI Europe which is supported in part by the European food industry.

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Appendix. List of participants at the workshop on the application of post-market monitoring to novel foods, 15–17 November 2006, Barcelona, Spain

Dr. Peter Abbott	Food Standards Australia New Zealand (FSANZ)	AU
Dr. Vincent Amanor-Boadu	Kansas State University	US
Dr. Sandra Bausch-Goldbohm	TNO – Nutrition and Food Research Institute	NL
Prof. Sir Colin Berry	Consultant	UK
Prof. Heiner Boeing	German Institute of Human Nutrition (DIFE)	DE
Prof. Alan R. Boobis	Imperial College	UK
Mr. Luc Bourbonniere	Health Canada	CA
Dr. Jaqueline Castenmiller	Food and Consumer Product Safety Authority	NL
Dr. Andrew Cockburn	Consultant	UK
Dr. Anne Constable	Nestlé	UK
Dr. Agnes Davi	Groupe Danone	FR
Dr. Nynke de Jong	National Institute of Public Health & the Environment (RIVM)	NL
Mr. Gareth Edwards	Consultant	UK
Prof. Karl-Heinz Engel	Technical University of Munich	DE
Mr. Andrew Foster	Taylor Nelson Sofres (TNS)	UK
Dr. Leng Heng	European Food Safety Authority (EFSA)	IT

Dr. Paul Hepburn	Unilever	UK
Dr. Tero Hirvonen	National Public Health Institute (KTL)	FI
Mr. John Howlett	Consultant	UK
Mr. Oliver Lindtner	Federal Institute for Risk Assessment (BfR)	DE
Ms. Päivi Mannerkorpi	European Commission – DG SANCO	BE
Prof. Bevan Moseley	Consultant	UK
Dr. Ian C. Munro	CanTox Health Sciences International	CA
Dr. Regina Oberdörfer	Bayer CropScience	DE
Dr. John O'Brien	Food Safety Authority of Ireland	IE
Prof. Gérard Pascal	National Institute for Agricultural Research (INRA)	FR
Dr. Barbara Petersen	Food and Chemicals Practice Exponent	US
Mr. Giles Quick	Taylor Nelson Sofres	UK
Dr. Claire Robertson	University of Westminster	UK
Ms. Annie-Laure Robin	Food Standards Agency (FSA)	UK
Prof. Ian Rowland	University of Ulster	UK
Prof. Sirpa Sarlio-Lähteekorva	Finnish Food Safety Authority	FI
Prof. Colette Shortt	McNeil Nutritionals Europe	UK
Dr. Eugene van Puijenbroek	Dutch Pharmacovigilance Centre LAREB	NL
Ms. Ruth Veale	The European Consumers' Organisation (BEUC)	BE
Dr. Philippe Verger	National Institute for Agricultural Research (INRA)	FR
Dr. Hans Verhagen	National Institute for Public Health & the Environment (RIVM)	NL
Dr. Jean-Michel Wal	National Institute for Agricultural Research (INRA)	FR

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