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Opinion of the Scientific Committee on Food on a report on Post Launch Monitoring of "yellow fat spreads with added phytosterol esters"

(expressed on 26 September 2002)

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1. TERMS OF REFERENCE

With reference to the post launch monitoring plan presented by Unilever in response to Article 3 of Commission Decision 2000/500/EC, the Scientific Committee on Food (SCF) is invited to express an opinion on the report delivered by Unilever and, in particular on the conclusions presented in the report.

2. BACKGROUND

The SCF expressed an opinion in April 2000 on the safety assessment of the use of phytosterol esters in yellow fat spreads (SCF, 2000). The Committee concluded that the use of phytosterol esters in yellow fat spreads at a maximum level corresponding to 8% free phytosterols is safe for human use. Furthermore it was the opinion of the Committee that the applicant (Unilever) should perform, in accordance with chapter XI in the Annex of Commission Recommendation 97/618/EC, a post-marketing surveillance study to obtain data on consumption and further investigation of possible health effects, among others the effects on plasma beta-carotene levels.

As part of the Commission Decision 2000/500/EC on authorising the placing on the market of "yellow fat spreads with added phytosterols" as a novel food or novel food ingredient under Regulation 258/97/EC, the applicant was obliged to collect data in order to estimate the extent to which the product is reaching its target group, i.e., people who try to control their elevated blood cholesterol, and to estimate exposures to phytosterols from this source in other population groups.

3. DESCRIPTION OF THE POST LAUNCH MONITORING (PLM) STUDY

The applicant has developed a new scheme (Unilever, 2002) to encompass the EC Decision requirements. It tackled as a starting reference the classical post-marketing surveillance (PMS) system, which is the system in place for monitoring of the known and unknown side effects of pharmaceuticals. This PMS requires the results be reported regularly to the regulatory agencies, it operates in a scenario where access to medicines is carefully controlled through the issue of prescriptions and availability through pharmacies or hospitals, and with physicians and pharmacists playing a main role as sources of information. In contrast, foods are widely available without prescription, mainly through retail outlets, and without participation of experts in food safety. Thus, PMS system for drugs is not directly applicable to foods.

In the absence of clear guidelines on how to carry out PMS for foods the applicant has applied a so-called Post Launch Monitoring (PLM) with some analogies to PMS. The main source of

information for the PLM scheme (Unilever, 2002) has been through consumer telephone care lines, and commissioning of market surveys to check that consumer usage patterns are consistent with predictions.

This PLM scheme has been applied only to the product manufactured with the Unilever-internal-quality-standards with raw materials conforming to the Committee approved specification (SCF, 2000). Actually, monitored products were spreads containing phytosterol esters referred to as "pro.activ."

The study has been developed using independent market research companies to gather real purchase data from consumers in The Netherlands, UK, France, Germany and Belgium, which are the major markets for pro.activ. The number of registered households varied according to the size of the population in each country (3000 in Belgium, 12,000 in Germany). Market research data up to 1 April 2001 were presented from about 2000 households in total.

The data provide information on both what and when the households buy, and what demographic group the purchaser belongs to. Panel members are not aware of which purchases are being monitored thus allowing them to provide both real purchase patterns and supply a link between purchase data and consumer type.

According to the applicant, the following three main questions were faced:

1. Is the product used as predicted/recommended?

2. Are known effects and side effects as predicted?

3. Does the product induce unknown side effects?

4. RESULTS

4.1 Use of the product

Results showed that 75 to 95% of purchasers were over 45 years old. Between 66 to 90% of regular purchasers and 62 to 82% of all people purchasing the product came from one- or two-persons households. There were no children in 79 to 91% of the households purchasing the product. Eighty-seven to 96% of regular purchasers had no children living at home.

The daily intake per household (based on the number of packs bought during a 12- to 13-week period, deliberately chosen at the end of the period being reviewed) was between 3 g/day (France) and 12 g/day (The Netherlands/Germany). For the regular users a more consistent pattern of usage was observed, with median intakes per household between 15 and 18 g/day.

The upper (95^{th} percentile) intake in all users was between 21 g/day (France) and 33 g/day (Belgium). For all regular users the upper intakes were between 27 g/day (France) and 45 g/day (The Netherlands).

It can be outlined that, with the exception of Germany, the intake estimates for one-person households were similar to those of larger (two to four) households, indicating that the use of the product was predominantly by one person per household.

4.2 Known effects and side effects

A long-term study on safety and efficacy of phytosterol esters in 185 volunteers following controlled intake of 20 g/day of a spread containing phytosterol esters (equivalent to 1.6 g sterols/day) over a one-year period was described (Hendriks *et al.*, 2001). Results were in agreement with a number of other clinical studies (SCF, 2002) and consistently demonstrated a reduction in the blood total and LDL-cholesterol levels – the known effects. The only side effect observed has been a reduction in the absorption of the most lipophilic carotenoids (e.g. beta-carotene).

In another study (Noakes *et al.*, 2002) (and see SCF, 2002) serum carotenoids levels were monitored in volunteers consuming specific amounts (≥ 5 daily servings) of fruit and vegetables in addition to phytosterol-enriched spreads over a 3-week period. This showed that the additional fruit/vegetables serving was effective in maintaining carotenoid levels when consuming spread-containing phytosterol esters.

4.3 Unknown side effects

All the Unilever operating companies have well-established telephone care lines in place for their products, in which consumer comments and complaints are answered and monitored. This constitutes an integrated network system that the company has established worldwide and that has been used in the present case. An additional training of the staff on collection of information on unexpected side effects from consumers has been undertaken.

Nearly 84,000 contacts to the care lines were registered during the first year of marketing, 70% of them during the first 7-month period, although an increment of sales during the shorter second period. Around 2% (1673 calls) were complaints, including 227 calls which were related to health issues.

For 148 calls a causal relationship could not be excluded but in no case could an association of the reported adverse symptoms be explained by the known properties of the sterol molecules. The majority of reports have been related to gastrointestinal effects (covering a wide range of self-diagnosed conditions such as diarrhoea and constipation) and skin conditions (broad in nature and with no clear patterns emerging), and the remaining calls covered a range of self-reported miscellaneous conditions.

Complaints were highest during the first few months after introduction into the market.

The conclusion is that reports to date do not indicate adverse effects associated with phytosterol intake.

4.4 Overall conclusions from the applicant regarding the PLM of pro.activ

The following main overall conclusions were drawn by the applicant:

A. The product is being bought by the target population but intakes are lower than the assumptions made in the original Novel Food submission (see SCF, 2000).

B. Long-term use of plant sterol-enriched spreads results in a reduction in the serum levels of the most lipophilic carotenoids but this is less than either the individual variation or the seasonal variation in carotenoid levels.

C. Carotenoid levels can be maintained by incorporating the use of plant sterol ester-enriched spreads into a healthy diet rich in fruit and vegetables.

D. Where available pro.activ users are also consuming plant stanol ester products (spread and non-spread products).

E. Given the extensive exposure to pro.activ in Europe the number of health-related calls has been small, predominantly from the UK and The Netherlands. These reports cover a broad range of self-reported conditions that are well within the normal occurrence of these conditions in the general population with no clear patterns emerging.

F. No evidence of occurrence of adverse health effects providing further support for the safe and effective use of pro.activ.

5. DISCUSSION

The overall conclusions drawn by the applicant, although they might be acceptable in general terms, cannot be drawn from the reported study directly as such but require some modification and clarification as discussed below.

As claimed by the petitioner there are no clear guidelines on how to carry out PMS or PLM for foods under a safety assessment perspective. This makes difficult to undertake studies in this field and the monitoring of safety-related aspects. A real need to establish general guidelines for this type of studies is thereby detected.

The Committee agrees that the observed use of the product is lower than was anticipated (see point A in section 4). Actually, market research data show median intakes of 15-18 g for regular consumers, which are less than the 20-30 g/day anticipated when the original submission was made. The same can be said with respect to the 95^{th} upper intakes, as observed values are 50% or less than those previously anticipated. This was not totally unexpected because anticipated figures considered consumption figures for total yellow fat spreads as a more prudent high intake scenario, rather than intakes of low-fat high-PUFA spreads.

The applicant concluded (see D) that some pro.activ consumers were also using products containing phytostanol esters, where these were available. This intake was not measured as it was not under the scope of the study. However, this is an interesting observation, out of the scope of what was required from the applicant, that has to be taken into account for future recommendations when PMS or PLM studies would have to face a more complex situation, with several different plant sterol-enriched foods, different sterol types and, not least important, from a number of different producers.

The results of the PLM study show that the product is purchased predominantly by adults over 45 years old and that regular purchasers are predominantly from one- or two-persons households and with no children living at home. While the Committee agrees that these results are compatible with the conclusion that the product is being bought by the target

population, the study design did not permit a direct evidence of this. The extent of consumption by children has not been specifically investigated. However, the similarity between consumption by one-person household and larger households suggests the predominant use is by one person per household, presumably to try to control elevated blood cholesterol levels.

In addition to this PLM study, new information on efficacy in clinical well-controlled studies was presented by the petitioner. It was not information drawn from the more real situation of intake by current consumers freely purchasing the product, e.g. in the supermarket. Reported results are in agreement with a number of other clinical studies (SCF, 2002) and consistently demonstrated a reduction in the blood total and LDL-cholesterol levels – the known effects. The reduction of the most lipophilic carotenoids has been the only observed side effect (see B). This observation fits well with several other studies (SCF, 2002) but a reduction in blood beta-carotene levels of around 20% (SCF, 2000) cannot be qualified as slight. This can be a nutritional problem in some particular cases (SCF, 2000) although is not being considered a problem relative to the potential benefits that subjects having high levels of circulating LDL-cholesterol may obtain (SCF, 2002). The Committee considers particularly reassuring a situation where carotenoid levels can be maintained by incorporating the use of plant sterol ester-enriched spreads into a healthy diet rich in fruit and vegetables (see C).

Furthermore, the applicant refers to studies on the effect of spread-containing phytosterol esters when used in conjunction with cholesterol-lowering drugs i.e. statins and fibrates (Neil *et al.*, 2001; Nigon *et al.*, 2001; cited in Unilever, 2002) indicating that phytosterol esters can be used to provide "additional" cholesterol-lowering effect. There were no unexpected side effects. Further consideration on these situations is included in a parallel opinion of the Committee (SCF, 2002).

With respect to other unknown side effects, it should be first emphasised that the appropriate toxicological studies in animals and human studies had already been evaluated (SCF, 2000). The present exercise is referring only to any marginal evidence that could be eventually drawn from PLM. This type of monitoring is not standard practice in the food industry, and no guidelines exist on how to monitor for possible unknown side effects. Reports obtained to date do not reveal a significant concern on adverse health effects. Studies were limited to intake estimations and self-reporting calls received from consumers at Unilever's telephones. The figure of 148 calls out of 84,000 contacts that were registered for which a causal relationship could not be excluded, cannot be considered of concern (see E), since the types of complaints are diverse and non severe, and because in no case could the reported adverse symptoms be explained by the known properties of the molecule. The Committee agrees that no evidence was obtained on occurrence of adverse health effects (see F).

6. CONCLUSION

The present opinion outlines the difficulty of the applicant of not having available clear guidelines on how to carry out PMS or PLM for foods. This makes it difficult to undertake studies in these fields and the monitoring of safety-related aspects. In this respect the reported study constitutes a valuable piece of reference in this growing area.

Given the extensive exposure to the product in Europe the number of health-related calls received from the consumers has been small. No evidence was obtained from PLM on

occurrence of adverse health effects from the current intake of marketed spread-containing phytosterol esters.

Known effects and side effects shown by reported clinically controlled studies were as predicted: Reduction in the levels of circulating LDL-cholesterol accompanied by a reduction of most lipophilic carotenoids, which appears to be able to be balanced by a healthy diet rich in fruit and vegetables.

In summary, the Committee concludes that despite the difficulties previously discussed, the applicant has fulfilled the above mentioned EC mandatory requirement of developing a post-marketing surveillance study to obtain data on consumption of phytosterol esters in yellow fat spreads and further investigation of possible effects, among others the effects on plasma beta-carotene levels.

7. FURTHER STATEMENT

The Committee concludes that the data from these PLM studies provided valuable information, in particular with respect to product consumption, which complemented that obtained in the pre-market safety evaluation studies. The Committee recommends that consideration should be given to developing guidance for the future design and conduct of such studies.

8. REFERENCES

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