COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT FOR THE ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES ON TOXICOLOGICAL ASPECTS OF A SUBMISSION ON SHORT AND LONG CHAIN TRIACYL GLYCEROL MOLECULES (SALATRIMs) – A FAMILY OF LOW CALORIE FATS SUBMITTED FOR APPROVAL UNDER THE EC NOVEL FOOD REGULATION

Introduction

1. In 1997 we issued a statement (Committee on Toxicity, 1997) on specific aspects of a submission made to the Advisory Committee for Novel Foods and Processes (ACNFP) on Salatrims, a family of low calorie fat materials. We had been asked by ACNFP to comment on the toxicological aspects of the data provided at that time under the voluntary system that existed for the evaluation of novel foods.

2. We concluded that there were three areas of concern that needed to be addressed further, namely:

i) additional pharmacokinetic studies were required to evaluate blood levels of short chain fatty acids in volunteers following consumption of individual Salatrim products before any conclusions could be drawn regarding the teratogenic risk of Salatrims;

ii) a No Observable Adverse Effect Level (NOAEL) should be determined for effects of Salatrims on enzyme markers for liver dysfunction in humans; and

iii) a NOAEL should be determined for effects of Salatrims on gastrointestinal function in humans.

3. The EC Regulation on Novel Foods and Novel Food Ingredients was introduced in May 1997, after the initial consideration of Salatrims in 1995-1997. As Salatrims were not on the market in Europe at that time, they are regarded as novel foods and therefore they

require clearance under the Regulation before they can be sold in Europe. An application has now been made to the UK Competent Authority for such clearance (Cultor Food Science, 1999) and ACNFP has asked for our further advice on the additional information and analysis included in the submission to meet the concerns that we identified earlier.

4. Our first statement described the toxicological and clinical data available on Salatrims in 1997. This statement, which needs to be read in conjunction with our previous opinion, discusses the additional data and analyses provided in the submission made under the Novel Food Regulation in response to the concerns that we had identified.

Levels of short chain fatty acids and possible teratogenic risk

5. The Committee had previously expressed a concern that the release of butyric acid from Salatrim which is rich in this short chain fatty acid might be sufficient to cause a rise in plasma butyrate levels. This possibility needed to be examined in the light of in *vitro* data on possible teratogenic effects of high levels of butyric acid. A new study.has been conducted (Pronczuk, Lipinski and Hayes, 1999) in which the post-prandial response to a load of 30 grams (g) of butyrate-based Salatrim (known as 4SO) was investigated to determine, amongst other effects, whether free butyrate would reach the general circulation. Plasma was analysed for butyric acid at regular intervals up to 360 minutes after dosing and at no time could free butyric acid be detected.

6. The Committee was satisfied by these data.

Effects on enzyme markers for liver dysfunction in humans

7. The Committee had asked that further information be provided to enable a NOAEL to be set for the effects of Salatrims on enzyme markers of liver dysfunction seen previously in the free-living clinical study. The company has provided further statistical analyses of the serum enzyme data from this study and expert assessments of the implications of those statistical analyses.

8. Small, statistically significant increases were recorded in the mean activities of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at the beginning of the exposure period in the free-living clinical study, although the mean values for the treatment groups did not fall outside the normal ranges for these enzymes at the laboratory conducting the study. The Committee noted that there was some concordance in the increases in liver enzymes AST and ALT within individuals and that some temporal trends were apparent. The Committee had also noted that it was possible that the individuals who withdrew from the study may have been atypical and that this could have contributed to the variability of the data. However, the company submitted information that shows that those individuals who withdrew from the study, did so mainly because of adverse gastro-intestinal effects resulting from consumption of 60 g/day Salatrim. In

addition, further analysis of the enzyme activities for those withdrawing from the study in comparison to those remaining shows that there were no significant differences in changes above baseline for serum hepatic enzyme activities whether or not those subjects withdrawing from the study were included.

9. In addition, data from a further study conducted by Nestel and colleagues (1998) were provided. In this five-week crossover study, following a low-fat control phase, subjects consumed diets containing margarine rich either in Salatrim or in palm oil ('palmitate'). These subjects were selected on the basis of their having an elevated blood cholesterol level and the study was designed primarily to provide information on effects of Salatrim on blood lipid levels. However, additional analyses of serum enzymes from blood samples taken pre-dose and at the end of each dietary phase showed that mean activities of AST and ALT, and other indices of hepatic function (γ-glutamyl transferase, alkaline phosphatase and lactic dehydrogenase) were no different at the end of the Salatrim and 'palmitate' dietary phases. Small increases in serum enzymes were noted after the 'palmitate' dietary phase in some subjects, which were of a similar magnitude to those seen in some subjects consuming Salatrim in the free-living clinical study described above.

10. The Committee concluded that consumption of high doses of Salatrim did result in slight increases in AST and ALT activities in serum, but noted that these increases were within the normal reference range. The further analyses of the enzyme data satisfied the Committee that there were no differences in the trends seen whether those withdrawing from the study were included or not. These enzyme changes, in the absence of any other indications of liver damage, were not considered to represent a clear toxic effect. The data from the five-week crossover study (Nestel et *al*., 1998) provided reassurance of a lack of any clear adverse hepatic effect. However, the Committee noted that the reported studies did not include investigations in children or in those with pre-existing liver disease.

Effects on gastrointestinal function in humans

11. The Committee had noted previously that gastrointestinal effects had been recorded in a number of subjects consuming Salatrim and had asked that further information be provided to enable a NOAEL to be determined. A further analysis of these observations was submitted by the company. The company suggested that the gastrointestinal disturbances reported were the consequence of sudden changes from an absorbable diet to one containing significant amounts of unabsorbable material. Metabolism of Salatrims rich in short chain fatty acids might result in rapid release of cholecystokinin, which would lead to slow gastric emptying, nausea and bloating. Analysis of the reasons for subjects withdrawing from the study shows that adverse gastrointestinal symptoms (such as nausea, cramps and gas) were the predominant reason for withdrawal from the study in the 60 glday Salatrim group. However, there was no clear evidence of any increase in the incidence of such effects at intakes of 30 or 45 glday Salatrim.

12. The Committee considered that the gastrointestinal disturbances seen after consumption of high doses of Salatrim could be the result of individual intolerances, noting the considerable variation between individuals and their tolerance to fibre and other poorly digested substrates. Nevertheless, these effects were seen in a significant proportion of individuals after consumption of 60 g/day Salatrim and needed to be considered in the context of estimates for adults of a mean intake of 11 g Salatrim/day and of a 97.5th percentile intake of 33g Salatrimlday. Salatrims are intended for use in reduced calorie foods aimed at individuals choosing a diet for the control of weight (Cultor Food Science, 1999). The main target consumers would be adults over 16 years of age and the intake estimates therefore were derived only for adults using commercially available databases on UK food consumption in conjunction with information on the types of food in which Salatrim would be used and the likely levels of inclusion. The application under the Novel Food Regulation is restricted to use in confectionery and baked goods only.

13. The Committee was of the view that the gastrointestinal effects seen were likely to be linked to intolerances to large amounts of this material rather than any specific toxic effect. However, gastrointestinal effects might be more common in children because of their relatively higher nutrient requirement and dietary intake. The Committee further concluded that it was not possible to set any no effect level on the basis of such subjective end points.

Conclusions

14. On the basis of the new data and analyses now provided, the Committee concluded that:

i) consumption of Salatrim did not result in any elevation in plasma butyrate levels and thus did not pose any teratogenic risk;

ii) consumption of high doses of Salatrim did result in slight increases in AST and ALT activities in serum, although these increases were within the normal reference range. There were no differences in the trends seen whether those dropping out of the study were included or not. These changes in enzyme activities, in the absence of any other indications of liver damage, were not considered to represent a clear toxic effect. The data from the five-week crossover study in humans provided an additional reassurance of the lack of any clear adverse effect;

iii) the gastrointestinal effects reported were likely to be linked to individual intolerances to large amounts of this material rather than to any adverse toxic effect. Furthermore, it is not possible to set any no effect level on the basis of such subjective end points.

15. The Committee noted that neither children nor those with pre-existing liver disease were included in the trial groups. However, the Committee understands that products containing Salatrim would be aimed at adults choosing a diet for the control of weight.

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References

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