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

STATEMENT ON SUPPLEMENTS CONTAINING FRENCH MARITIME PINE BARK EXTRACTS

Introduction

1. In 1998 we were asked to consider a submission which had initially been made to the Advisory Committee on Novel Foods and Processes (ACNFP) seeking food safety clearance of an extract derived from the bark of the pine tree (*Pinus pinaster*). The French maritime pine bark extract is sold in the form of a dietary supplement. The ACNFP had advised that since the extract has been on sale in the UK and other European countries for a number of years, it would not be considered a novel food. However, the ACNFP did have some concerns regarding the toxicological data included in the submission and it was therefore referred to this Committee.

2. In our consideration of the submission we identified problems with the data received, as some of the information was in the form of brief summaries of old, unpublished studies. In addition, it was not clear that the studies had used material which corresponded to that currently marketed. We therefore indicated that an adequate specification of the extract should be provided before any further work was undertaken. The deficiencies in the reporting or execution of the toxicological studies led us to recommend that some studies should be repeated or appropriate new studies be performed in order to clarify aspects of the toxicity of the extract. In particular we had concerns about a report, in an abstract, of lesions occurring in the brain of dogs after a 6-month feeding study, about potential teratogenic/foetotoxic and endocrine/reproductive effects and also the possible mutagenicity and allergenicity of the extract. Our conclusions were recorded in the form of a statement (Committee on Toxicity, 1998).

Consideration of new data

3. We have since received additional documentation which comprises:

a) more detailed specifications of the product (Rohdewald, 1999a);

b) history of the production and nomenclature of the extract (Gulati, 1999);

c) a new mutagenicity study (Wollny, 1998);

d) a copy and certified translation of the report of the original 6-month feeding study in dogs (International Bio-research, 1975);

e) an expert opinion of the report of the original 6-month feeding study in dogs (McLean, 1999); and

f) a statement as to the absence of protein in the product (Rohdewald, 1999b).

Specifications

4. We are satisfied that, within the limitations of the analytical methodology, the specifications and analytical data submitted provide adequate assurance of the consistency of batches of French maritime pine bark extract prepared by current production methods (Rohdewald, 1999a). Although there is an extensive history of production of the extract, the analytical data are not available to demonstrate that the extract used in early studies is similar to that currently produced (Gulati, 1999).

Mutagenicity

5. We have been informed that the recently completed mutagenicity assay (Ames test) has been reviewed by the Secretariat of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment who concluded that the extract was non-mutagenic in the assay. Having seen the report of this study (Wollny, 1998), we endorse this conclusion.

The 6-month toxicity study in dogs

6. When we first considered the toxicity data available for the French maritime pine bark extract the only information on this study, carried out in 1975, was a short abstract. A statement about the development of lesions in the brains of dogs raised concerns that were not resolved by the other available toxicity data. Unfortunately, the full report of the study did not remove these concerns (International Bio-research, 1975). Although the lesions of the brain and spinal cord occurred only in the group of animals receiving the highest dose, we note that the study pathologists had not been able to determine whether the lesions were treatment-related or were artefactual, possibly having resulted from some difference in the post mortem processing of the tissues. Lack of detail in the report meant that we were unable to make any judgement on this issue.

7. Other aspects of this study were of concern. The dosing schedule at the start of the treatment had involved the oral administration of 0, 60, 150 and 500 milligram of the extract per kilogram of body weight (mglkg b.w.) on only six days of each week. Six weeks before the end of the study the top dose was increased to 1000 mg/kg b.w. administered continuously, which we assume to be on seven days per week. This variation to the dosing schedule of the top dose group makes comparisons with the two lower dose groups difficult to interpret.

8. It has been suggested to us that the administration of six doses per week would have been considered reasonable at the period when the study was carried out (McLean, 1999). This is not our opinion, as at that time it was recognised that the use of such a schedule could offer a period of recovery from any adverse effects of the test substance. Since the report does not provide information to indicate at what stage of the weekly dosing schedule animals were killed or samples were taken for haematology and clinical chemistry it is possible that some of the changes recorded during the study and at its termination may have been minimised by an intervening period of recovery.

9. In addition to the lesions of the nervous system there were effects on the heart rate and body weight gain in the top dose group. These were restricted to that group. However, some changes, e.g. in organ weights, in leucocyte counts and in blood triglyceride and glucose concentrations were reported as occurring in all the treated groups, although there was evidence of a sex-specificity of changes in some organ weights.

10. The deficiencies in the study mean that we reiterate our opinion that this study needs to be repeated in order either to dismiss or to substantiate the concerns that it has raised.

Allergenicity

11. We considered a statement which indicated that no nitrogen had been detected in three batches of the French maritime pine bark extract by elemental analysis and that no protein had been detected by an electrophoretic technique (SDS-PAGE). Without information on the procedures involved and the Limits of Detection for the samples the statement does not provide any reassurance as to the absence of allergenic protein in the extract (Rohdewald, 1999b).

Reproductive toxicity

12. Neither new data nor original full study reports have been submitted to address our concerns about possible teratogenicity and endocrine and/or reproductive effects of the French maritime pine bark extract. We have been informed that a consultation with industry is in progress about the labelling of the product in order to indicate that it is a preparation for adults but should not be taken during pregnancy or breastfeeding. We have been asked whether it would **be** sufficient to advise that it not be taken by children younger than 8 years of age. In the absence of data that provide reassurance in these matters we would not recommend that the suggested age be lowered from that of adulthood.

Conclusions

(i) We accept that, within the limits of the techniques used, the analytical data submitted on batch-to-batch variation of the French maritime pine bark extract provide evidence of consistency of the currently manufactured product.

(ii) The full report of the 6-month dog study has not removed our concerns about the possible adverse effects resulting from the administration of French maritime pine bark extract. We do not consider that this study is adequate for the determination of a No Observed Adverse Effect Level. Therefore, we reiterate our view that it is necessary to repeat this study to present-day testing guidelines.

(iii) On the basis of the studies originally and recently submitted we consider that the extract is non-mutagenic.

(iv) We would wish to see the experimental details, including the Limits of Detection, of the studies undertaken to detect any protein in the extract before accepting that allergenic proteins are absent.

(v) We repeat our recommendation that the original reports of the high dose embryo-foetal studies be provided and that in *vitro* and/or short-term in vivo studies be undertaken to address the question of possible endocrine or reproductive effects of the extract. In the interim, we support the suggested labelling of the product to indicate that it should be taken only by adults but not by pregnant women or nursing mothers.

July 1999

COT Statement 1999105

References

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