AGENCE FRANÇAISE
DE SECURITE SANITAIRE
DES ALIMENTS
THE FRENCH FOOD
SAFETY AGENCY

DIRECTOR- GENERAL

Maisons-Alfort, 23 January 2004

OPINION

of the French Food Safety Agency regarding the assessment of the safety in use of a food supplement combining three active compounds: "lacto-lycopene" (a lycopene-rich tomato extract combined with lacto-proteins), an isoflavone-rich soy extract and vitamin C

On 12 June 2003, the Directorate-General for Competition, Consumer Affairs and Fraud Control (*DGCCRF*) requested, in a letter dated 6 June 2003, that the French Food Safety Agency (AFSSA) assess the safety in use of a food supplement combining three active compounds: a lycopene-rich tomato extract combined with lactoproteins called "lacto-lycopene", an isoflavone-rich soy extract and vitamin C.

The request concerns a food supplement, intended for cosmetic use, formulated "to counter age-related skin changes".
Each tablet contains:

- 60 mg of lacto-lycopene™, a lycopene-rich tomato extract with lactoproteins, supplying 2 mg of lycopene,
- 41.5 mg of soy extract containing 41% isoflavones, or 16.7 mg of isoflavones primarily in the form of glycosides (including 28% genistein, 10% daidzein and 2% glycitein),
- 20 mg of vitamin C (ascorbic acid).

These three active compounds, lycopene, isoflavones and vitamin C, were "selected for their synergistic effect on skin density".
The daily intake recommended by the petitioner is 2 to 3 tablets per day, over periods of up to 6 months.
The target population is "adult women, particularly those concerned about age-related skin problems, and often nearing menopause".
Several claims were made:

- "Nutritionally redensifies the skin. Tones and restores density to the skin",
- "Exclusive formula with Lacto-Lycopene™, soy extract and vitamin C to fortify collagen and glycans in the skin",
- "Scientifically shown to be effective for the face and body",
- "Helps maintain skin firmness and density, particularly during hormonal ageing",
- "Proven effectiveness. Improved firmness after 2 months; redensification of deep skin layers scientifically demonstrated using biophysical measurements".

After consultation with the Scientific Panel on Human Nutrition, which met on 20 November 2003, AFSSA is issuing the following opinion:

On aspects regarding the safety in use of the food supplement:

Considering that vitamin C is on the list of substances that can be used for the manufacture of food supplements (Directive 2002/46/CE); that the daily intake of vitamin C reached by taking 3 food supplement tablets, or 60 mg, corresponds to the recommended daily allowance of this vitamin; that consumption of this amount is not likely to lead to any risk of exceeding the safety limit (1000 mg/day);

Considering that lycopene is authorized as a food colouring agent (E160d) in the European Union (modified Decree of 2 October 1997); that it is used as an ingredient, Lyc-O-mato® (tomato oleoresin extract), in the formulation of this food supplement; that the TNO (Netherlands Organization for Applied Scientific Research) has shown that Lyc-O-mato® 6% is safe to use and that this has been further confirmed by additional, unpublished studies conducted by the

23, Avenue du
Général de Gaulle
BP 19, 94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 90 05
www.afssa.fr

REPUBLIQUE
FRANÇAISE

petitioner; that the daily dose of lycopene reached by consuming 3 tablets is 6 mg, an intake level higher than that commonly observed in European countries (1 to 2 mg/day); that nevertheless, on the basis of the maximum amount at which no side effects are observed (NOAEL [No observed adverse effect level] of 270 mg/kg), consuming this amount poses no risk to the consumer, the safety-in-use factor is at least 650 for a young subject weighing less than 15 kg and 2500 for an adult subject weighing 55 to 60 kg; that the toxicology studies were carried out using Lyc-O-mato® 6%, whereas it is Lyc-O-mato® 10% that was used in the manufacture of the food supplement on the basis of extrapolation; that Lyc-O-mato® is used in a specific form, Lacto-Lycopene™, that presents higher bioavailability but a potential risk of allergy due to the presence of cow's milk proteins; that this risk was not mentioned by the petitioner whatsoever;

DIRECTOR- GENERAL

Considering that the daily amount of soy isoflavones equivalent to an intake of 3 food supplement tablets is 52.8 mg; that this amount can be considered acceptable in terms of safety, since only 50% of this amount is likely to pass into the blood stream; that this amount is comparable to the amount of isoflavones consumed in a traditional Asian-style diet; and the soy extract used received GRAS[1] status from the FDA[2] in 2000;

Considering that the safety in use of the food supplement was not specifically proven but extrapolated from that of the three active compounds present in the food supplement; that its safety in use may nonetheless be regarded as certain;

Considering that the manufacturing processes and specifications for the food supplement are clearly defined: ingredients, manufacturing stages, quality control and assurance, packaging and storage;

Considering aspects of the anti-skin-ageing effectiveness of the three active compounds found in the food supplement:

Considering that oxidative stress as well as the accumulation of radical oxygen species are recognized as the primary causes of skin ageing; that the antioxidant properties of the three active compounds present in the food supplement, vitamin C, lycopene and isoflavones, are generally allowed based on significant scientific literature that reports *in vitro*, and *in vivo* studies in animals, but rarely *in vivo* studies in humans; that additional studies on humans were conducted by the petitioner, but have not yet been published:

- the antioxidant potency of vitamin C, as well as its effect when coupled with vitamin E, are well documented: it helps to transform procollagen into collagen, reduce actinic patches (age spots), and heal skin following injuries;
- lycopene is the most powerful antioxidant of the carotenoid family and this property has essentially been proven *in vitro*; with regard to the skin, a study in volunteers has shown that, after 10 weeks of intake, lycopene (lycopene + olive oil *versus* olive oil) brought about a 40% reduction in ultraviolet-induced erythemas; moreover, a study carried out by the petitioner shows, on a reconstructed skin model, epidermal gene expression coding for "protection and epidermal differentiation" factors (metallothionein, tissue inhibitor of metalloproteinase, heparin-binding epidermal growth factor inhibitor);
- the antioxidant properties of isoflavones are related to their phenolic structure and are not specific to genistein, as indicated by the petitioner; some recent studies in mice, although methodologically imperfect, have shown an increase in levels of certain antioxidant enzymes (superoxide dismutase, glutathione peroxidase and glutathione reductase) in the skin under the effect of genistein; biochemical tests performed by the petitioner showed that genistein (at concentrations 10 times higher than circulating concentrations) inhibited elastase and collagenase activities, without any effect on hyaluronidase; topically administered genistein inhibited the MMP-1 marker for light-induced skin ageing;
- the antioxidant effect of the food supplement has been convincingly evaluated on a human skin model taken from menopausal women: stimulation of cell proliferation and

23, Avenue du Général de Gaulle
BP 19, 94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 90 05
www.afssa.fr

REPUBLIQUE
FRANÇAISE

[1] GRAS: Generally Recognised As Safe
[2] FDA: Food and Drug Administration

increase in the levels of hyaluronic acid and in collagen by a mixture of the three active compounds (1.9 µM vitamin C, 0.68 µM lycopene and 2.5 µM genistein);

Considering that a clinical study was conducted on the food supplement; that it was a randomized, double blind, placebo-controlled study; that it involved two groups of 45 menopausal women over a period of at least 3 years; that the exclusion criteria included hormone replacement therapy, recent intake of food supplements, excessive tobacco or alcohol consumption, playing intensive sports and a vegetarian or high protein diet; that the food supplement intake was two tablets per day; that different methods for evaluating the effectiveness of the food supplement, namely, self-evaluation, clinical dermatological examination and biometrological assessments, were implemented at the beginning of the study, and after 3 and 6 months of intake;

DIRECTOR- GENERAL

Considering that the self-evaluation was conducted using a questionnaire; that it addressed the following criteria: moisture level, skin radiance and skin smoothness, firmness, resilience and reduction of wrinkles; that on the basis of these criteria, women from both the placebo and treatment groups noticed improvement in the condition of their skin, but no significant differences were detected between the two groups;

Considering that the parameters used for the clinical dermatological examination were: moisture level, skin dryness, softness, suppleness, tone, fine lines and wrinkles as well as skin radiance; that a slight improvement in skin radiance was observed in both groups but more rapidly in the treatment group (after 3 months *versus* after 6 months in the placebo group); that with regard to the other parameters, no differences between the placebo and treatment groups were detected;

Considering that the biometrological assessments carried out on the skin of the subjects studied changes in six parameters using equipment traditionally employed for evaluating the effects of cosmetics:

- the treatment group showed a slight increase in skin elasticity and the lipid layer compared to the placebo group, but these differences do not lend themselves to clinical interpretation;
- a study of the imprint of the skin's microrelief showed a significant smoothing effect ($p=0.06$) after 3 months in the two groups; the effect was maintained after 6 months only in the treatment group;
- complexion appeared darker, but identically in both groups; lycopene intake did not increase the intensity of orange skin shades but did increase the intensity of the yellows in the treatment group;
- an improvement in skin hydration was observed on the face, but not on the forearm, after 3 months;
- skin thickness was reduced equally in both groups, but water content increased significantly in the treatment group only;

Considering that a "consumer test" was carried out in 100 women from 45 to 55 years of age; that it was conducted in the form of telephone interviews after 1, and then 2 months of daily intake of two food supplement tablets; that the objective of the questionnaire was to evaluate the effectiveness of the food supplement and whether it supported the claims made; that the effectiveness of the food supplement and that of other products habitually used (anti-ageing or menopause aid food supplements) was evaluated on a scale of 0 to 10 and that the criteria tested were, among others, acceptability, overall satisfaction, firmness, density, moisture and softness of the skin; that the ratings assigned to the set of claims made as a whole were significantly higher ($p<0.5$) for the food supplement under evaluation than for the other habitually used products; that 78% of the women said they were satisfied with the food supplement without any indication provided on their satisfaction *vis-à-vis* the habitually used products;

23, Avenue du
Général de Gaulle
BP 19, 94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 90 05
www.afssa.fr

REPUBLIQUE
FRANÇAISE

Considering aspects of correspondence between the scientific data provided and the claims made:

Considering that the recommendations of the *DGCCRF* pertaining to the evaluation of cosmetic products state that "with the exception of cases in which a correlation with data obtained in humans can be established, evaluations made on a model other than human are not sufficient for determining the actual effect in the consumer"; that because of this, the results of the clinical study must constitute the foundation for proof of the claims made;

DIRECTOR- GENERAL

Considering that the conclusions of the scientific report on the clinical assessment of the effectiveness of the food supplement indicate that "the product promotes effective water absorption by various skin layers resulting in the maintenance of good skin turgor which itself results in a smoothing effect as demonstrated by analysis of skin microrelief, by an improved echogenicity in the treatment group and by the perceived sensation of a more radiant complexion; that it appears that, after analysis of all the results presented in the application, the claimed effectiveness of the food supplement lies, to a great extent, in subjective data (self-evaluation and consumer testing) and in a strong placebo effect, often encountered during studies on cosmetic products; that the designations of the five claims asserted are overly optimistic and are not entirely supported by the results presented:

- biometrological assessments showed that the main scientifically objective effect is significant hydration of the deep layers rather than the surface layers of the skin, resulting in improved turgor, giving the food supplement users the impression of having better skin tonus; very few beneficial effects were demonstrated regarding the other parameters studied (elasticity and skin surface lipid layer, skin radiance, forearm hydration and skin thickness);
- certain biometrological techniques are not suitable for testing the desired effects on the skin: the use of the Dermal Torque Meter® with a 20 mm diameter probe made it possible to test only the surface layers of the skin; moreover, the absence of accuracy as to the size of the gap used (1 or 5 mm) makes it difficult to interpret the results regarding any effect on the elasticity of the deep skin layers;
- the area used to make impressions of the skin microrelief was not specified, even if it is well known that the crow's foot area is generally the area used;
- suntans of certain subjects may have influenced the improvement of skin radiance, inasmuch as the study was carried out between March and September; moreover, the biometrological assessments were done on the forearms, whereas the clinical dermatological examination was conducted on the face, which does not facilitate comparison of the effectiveness of the food supplement on the face and the body;
- tests on cell cultures and skin explants show that the active compounds of the food supplement have a trophic effect, but no clinical parameter measured in subjects receiving the food supplement made it possible to demonstrate this effect;

- there is some concern that one of the claims which refers to hormonal ageing may create confusion between the effects of isoflavones on menopause symptoms and the antioxidant effects of isoflavones on skin that are attributed to the food supplement;

The French Food Safety Agency considers that:

- the safety in use of the food supplement has been demonstrated;
- the potential risk of allergy related to the presence of cow's milk proteins must be taken into account;
- the claims made are not justified given the data provided by the clinical study, despite the fact that certain *in vitro* data appear to be convincing; and

23, Avenue du
Général de Gaulle
BP 19, 94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 90 05
www.afssa.fr

REPUBLIQUE
FRANÇAISE

- the reservations expressed in the assessment of the food supplement by the Belgian authorities should be provided.

DIRECTOR- GENERAL

Martin Hirsch

23, Avenue du
Général de Gaulle
BP 19, 94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 90 05
www.afssa.fr

REPUBLIQUE
FRANÇAISE