EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to “hypo-caloric snacks (KOT products)” and “contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet” pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to "hypo-caloric snacks (KOT products)" and "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet" pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Ceprodi KOT, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to "hypo-caloric snacks (KOT products)" and "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet". The target population is overweight individuals who wish to reduce their abdominal fat. The applicant states that adipocyte size at the (subcutaneous) abdominal level correlates with abdominal fat mass, which is associated with metabolic complications. The evidence provided by the applicant does not establish that reducing subcutaneous adipocyte size at the abdominal level *per se* (i.e. independent of changes in body weight or body fat) would generally have an impact on the metabolic profile, or that changes in subcutaneous adipocyte size can be used as a surrogate measure of changes in visceral adipose tissue which could influence the metabolic profile. Therefore, the Panel considers that the evidence provided does not establish that reducing subcutaneous adipocyte size at the abdominal level is a beneficial physiological effect *per se* and concludes that a cause and effect relationship has not been established between the consumption of "hypo-caloric snacks (KOT products) for use in low-calorie diets for weight reduction" and a beneficial physiological effect related to "reducing subcutaneous adipocyte size at the abdominal level".

KEY WORDS

Hypo-caloric snacks, low-calorie diet, adipocyte size, abdominal fat, visceral adipose tissue, health claims

[1] On request from the Competent Authority of France following an application by Ceprodi KOT, Question No EFSA-Q-2011-00016, adopted on 14 September 2011.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from Ceprodi KOT, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to "hypo-caloric snacks (KOT products)" and "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet".

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and/or including a request for the protection of proprietary data.

The claimed effect is "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet". The target population proposed by the applicant is overweight individuals who wish to reduce their abdominal fat.

The applicant stated that adipocyte size at the (subcutaneous) abdominal level correlates with abdominal fat mass, which is associated with metabolic complications. To support this, the applicant referred to a cross-sectional study on the association between adipocyte size at different (subcutaneous) sites and total and abdominal (subcutaneous and visceral) fat mass in men and women.

Following EFSA's request for clarification, the applicant provided another cross-sectional study and three human intervention studies which investigated the relationship between subcutaneous adipocyte size, body weight, total body and visceral adipose tissue, and the metabolic profile. The information provided for one of the intervention studies was insufficient (abstract only) to allow evaluation by the Panel. The remaining two human intervention studies and the two cross-sectional studies did not provide information about the independent effect of reducing abdominal subcutaneous adipocyte size on the metabolic profile, nor on the use of subcutaneous abdominal adipocyte size as a surrogate measure for changes in visceral adipose tissue.

The Panel notes that the evidence provided by the applicant does not establish that reducing subcutaneous adipocyte size at the abdominal level *per se* (i.e. independent of changes in body weight or body fat) would generally have an impact on the metabolic profile, or that changes in subcutaneous adipocyte size can be used as a surrogate measure of changes in visceral adipose tissue which could influence the metabolic profile.

The Panel considers that the evidence provided does not establish that reducing subcutaneous adipocyte size at the abdominal level is a beneficial physiological effect *per se*.

The Panel concludes that a cause and effect relationship has not been established between the consumption of "hypo-caloric snacks (KOT products) for use in low-calorie diets for weight reduction" and a beneficial physiological effect related to "reducing subcutaneous adipocyte size at the abdominal level".

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BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Art 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 11/01/2011.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and/or including a request for the protection of proprietary data.
- On 11/02/2011, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- The applicant provided the missing information on 11/04/2011.
- The scientific evaluation procedure started on 20/04/2011.
- On 13/05/2011, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the clock was stopped on 17/05/2011 in compliance with Art. 18(3) of the Regulation (EC) No 1924/2006. The clock was restarted on 01/06/2011.
- On 06/06/2011, EFSA received the requested information as submitted by the applicant.
- During the meeting on 14/09/2011, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to "hypo-caloric snacks (KOT products)" and "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet".

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: "hypo-caloric snacks (KOT products)" and "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet".

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of "hypo-caloric snacks (KOT products)", a positive assessment of its safety, nor a decision on whether "hypo-caloric snacks (KOT products)" is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Ceprodi KOT, 67 boulevard de Courcelles, 75008 Paris, France.

Food/constituent as stated by the applicant

According to the applicant, the food that is the subject of the claim is "hypo-caloric snacks (KOT products) for use in low-calorie diets for weight reduction".

Health relationship as claimed by the applicant

According to the applicant, the main criterion of adiposity is the size of adipocytes, which reflects the capacity of fat cells to accumulate and mobilise triglycerides, and the reduction of the adipocyte diameter may lead to an improvement in the adverse health effects of an excess abdominal fat.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Contributes to reduce the adipocytes size at the abdominal level, in the context of a low-calorie diet".

Specific conditions of use as proposed by the applicant

According to the applicant, KOT products are intended for overweight subjects in the general population who want to decrease their adiposity at the abdominal level. In order to obtain the claimed effect, four "hypo-caloric snacks" should be consumed daily according to a pre-established menu in the framework of a low-calorie diet.

ASSESSMENT

Substantiation of a health claim requires: 1) definition and characterisation of the food/constituent, 2) definition of a claimed effect which is a beneficial physiological effect and, 3) an established cause and effect relationship between the consumption of the food/constituent and the claimed effect. A health claim cannot be substantiated if the outcome of any one of these assessments is unfavourable[5].

The characterisation of "hypo-caloric snacks (KOT products) for use in low-calorie diets for weight reduction" is not addressed in this opinion, but rather whether the claimed effect is a beneficial physiological effect.

1. Relevance of the claimed effect to human health

The claimed effect is "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet". The target population proposed by the applicant is overweight individuals who wish to reduce their abdominal fat.

The applicant states that adipocyte size at the (subcutaneous) abdominal level correlates with abdominal fat mass, which is associated with metabolic complications. To support this, the applicant refers to a cross-sectional study on the association between adipocyte size at different (subcutaneous) sites (i.e. abdominal, gluteal, femoral) and total and abdominal (subcutaneous and visceral) fat mass in men and women (Tchoukalova et al., 2008). However, no evidence was provided in the application that reducing subcutaneous adipocyte size at the abdominal level *per se* (i.e. independent of changes

[5] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

in body weight or body fat) would generally have an impact on the metabolic profile, or that changes in subcutaneous adipocyte size would generally predict changes in visceral adipose tissue which could influence the metabolic profile.

Following EFSA's request to clarify what would be the beneficial physiological effect of decreasing subcutaneous adipocyte size at the abdominal level *per se*, the applicant provided one cross-sectional study (Hoffstedt et al., 2010) and three human intervention studies (Larson-Meyer et al., 2006; Kong et al., 2010, unpublished; Rizkalla et al., 2011, unpublished) which investigated the relationship between subcutaneous adipocyte size, body weight, total body and visceral adipose tissue, and the metabolic profile. The information provided for one of the studies (Kong et al., 2010, unpublished, abstract only) was insufficient to allow evaluation by the Panel.

In the cross-sectional study by Hoffstedt et al. (2010) the association between mean visceral (omental) and subcutaneous adipocyte size and blood lipid, glucose and insulin concentrations, as well as markers of inflammation, was investigated in 80 women (21-64 years) with a BMI $\geq$35 kg/m^2. The Panel notes that this cross-sectional study does not provide information about the independent effect of reducing abdominal subcutaneous adipocyte size on the metabolic profile, nor about the use of subcutaneous abdominal adipocyte size as a surrogate measure for changes in visceral adipose tissue.

In the randomised controlled trial by Larson-Meyer et al. (2006), 48 overweight volunteers were randomly assigned to one of four groups for 6 months: control (100 % of energy requirements), 25 % calorie restriction (CR), 12.5 % calorie restriction plus 12.5 % energy expenditure through structured exercise (CREX), or 15 % weight loss by a low-calorie diet followed by weight maintenance (LCD). Weight, percent body fat, subcutaneous abdominal adipose tissue (SAT), visceral adipose tissue (VAT), intramyocellular lipid (IMCL), intrahepatic lipid (IHL), subcutaneous abdominal fat cell size (FCS), and insulin sensitivity index (S_i) were assessed at baseline and at month six of the study. VAT, FCS, percent body fat, and IHL were reduced in the three intervention groups ($p<0.01$) compared to control, whereas IMCL was unchanged. S_i significantly increased at month six in the CREX and LCD groups ($p<0.05$) compared to control. The improvements in S_i were related to weight loss, fat mass, and VAT, but not to IHL, IMCL, or FCS. The decrease in FCS was correlated with the decrease in body weight, percent fat, VAT, and SAT. However, the relationship between changes in FCS and VAT was no longer significant when only the three study groups which lost weight were considered. The Panel notes that body weight loss was associated to a reduction of all fat compartments (except for intramyocellular lipid), to a reduction of subcutaneous abdominal adipocyte size, and to an increase in insulin sensitivity. However, the Panel also notes that the reduction of subcutaneous abdominal adipocyte size was not correlated with the increase in insulin sensitivity or with the reduction of visceral abdominal fat. The Panel considers that this study does not support an independent effect of reducing abdominal subcutaneous adipocyte size on insulin sensitivity, nor the use of subcutaneous abdominal adipocyte size as a surrogate measure for changes in visceral adipose tissue.

One randomised controlled cross-over study (Rizkalla et al., 2011, unpublished) in 14 subjects (five women, 45±2.4 years, BMI=31.68±1.3 kg/m^2) investigated the effect of consuming two energy-restricted diets (1200 kcal/day) with different macronutrient composition ("high protein diet" vs. "conventional diet") on body weight, body fat, adipocyte size from subcutaneous peri-umbilical adipose tissue, blood lipids, blood pressure, blood glucose and insulin concentrations, insulin resistance, adipokines and markers of inflammation. Each diet was consumed for four weeks with an 8-week washout in between. Power calculations were not performed and the primary outcome was not identified. The effects of the two diets were compared using a multivariate analysis of repeated measures (MANOVA) followed by a post-hoc test. When the diet x time interaction was significant (e.g. as for adipocyte size), the effect of each diet was analysed separately for each arm with the Student t-test for paired samples. The Panel notes that this type of analysis is not appropriate for crossover designs and considers that no conclusions can be drawn about the relative effects of each dietary intervention on the outcome variables, including adipocyte size from subcutaneous peri-

umbilical adipose tissue. Correlations between changes in adipocyte size and changes in metabolic variables during the entire study period and during each dietary period were also assessed. The Panel notes that these correlations do not provide information about the independent effect of reducing abdominal subcutaneous adipocyte size on the metabolic profile (e.g. independent of changes in body weight, body fat, and/or visceral abdominal fat). The Panel considers that this study does not provide information about the independent effect of reducing abdominal subcutaneous adipocyte size on the metabolic profile, nor on the use of subcutaneous abdominal adipocyte size as a surrogate measure for changes in visceral adipose tissue.

The Panel notes that the evidence provided by the applicant does not establish that reducing subcutaneous adipocyte size at the abdominal level *per se* (i.e. independent of changes in body weight or body fat) would generally have an impact on the metabolic profile, or that changes in subcutaneous adipocyte size at the abdominal level can be used as a surrogate measure of changes in visceral adipose tissue which could influence the metabolic profile.

The Panel considers that the evidence provided does not establish that reducing subcutaneous adipocyte size at the abdominal level is a beneficial physiological effect *per se*.

The Panel concludes that a cause and effect relationship has not been established between the consumption of "hypo-caloric snacks (KOT products) for use in low-calorie diets for weight reduction" and a beneficial physiological effect related to "reducing subcutaneous adipocyte size at the abdominal level".

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The claimed effect is "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet". The target population proposed by the applicant is overweight individuals who wish to reduce their abdominal fat. The evidence provided does not establish that reducing subcutaneous adipocyte size at the abdominal level is a beneficial physiological effect *per se*.

- A cause and effect relationship has not been established between the consumption of "hypo-caloric snacks (KOT products) for use in low-calorie diets for weight reduction" and a beneficial physiological effect related to "reducing subcutaneous adipocyte size at the abdominal level".

DOCUMENTATION PROVIDED TO EFSA

Health claim application on "hypo-caloric snacks (KOT products)" and "contributes to reduce adipocyte size at the abdominal level in the context of a low-calorie diet" pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0294_FR). April 2011. Submitted by Ceprodi KOT.

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GLOSSARY AND ABBREVIATIONS

CR	calorie restriction
CREX	calorie restriction plus energy expenditure
FCS	fat cell size
IHL	intrahepatic lipid
IMCL	intramyocellular lipid
LCD	low-calorie diet
SAT	subcutaneous abdominal adipose tissue
S_i	insulin sensitivity index
VAT	visceral adipose tissue