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SCIENTIFIC OPINION

Statement on the safety of 'Cetyl Myristoleate Complex' as an ingredient in food supplements[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to update its opinion on the safety of 'Cetyl Myristoleate Complex' (CMC) as a novel food ingredient in the light of a new repeated dose 90-day oral toxicity study in mice. In its previous opinion of 2010, the Panel concluded that based on the available data, the safety of CMC as an ingredient in food supplements has not been established. This conclusion was based on the considerations that in the absence of appropriate data on absorption, distribution, metabolism and excretion, the provided toxicological data were insufficient. Whereas the applicant considers that the NOAEL of CMC in this new 90-day study was 1000 mg/kg body weight (bw), the highest dose tested, the Panel considers that this study and study report has many shortcomings to be a reliable source of information supporting the absence of adverse effects of the parent material CMC. The Panel concludes that the safety of 'Cetyl Myristoleate Complex' has not been established.

KEY WORDS

cetyl myristoleate complex, cetyl myristoleate, cetyl myristate, cetylated fatty acid, ingredient, novel food

[1] On request from the European Commission, Question No EFSA-Q-2012-00649, adopted on 31 May 2013.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Novel Foods: Karl-Heinz Engel, Ines Golly, Marina Heinonen, Pagona Lagiou, Rosangela Marchelli, Bevan Moseley, Monika Neuhäuser-Berthold, Annette Pöting, Seppo Salminen, Hendrik Van Loveren and Hans Verhagen for the preparatory work on this scientific opinion, and EFSA staff Wolfgang Gelbmann for the support provided to this scientific opinion.

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SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to update its opinion on the safety of 'Cetyl Myristoleate Complex' (CMC) with an intended daily intake of 3.3 g per person per day as a novel food ingredient in food supplements in the light of additional information provided by the applicant on a repeated dose 90-day oral toxicity study in mice.

'Cetyl Myristoleate Complex' consists of 50 % cetylated fatty acids, 48 % corn starch and 2 % silicon dioxide. The applicant proposed a daily intake of 3.3 g CMC [1.65 g cetylated fatty acids (CFAs)] which contains approximately 660 mg of both cetyl myristoleate and cetyl myristate, the two main compounds of CMC.

In its previous opinion of 2010, the Panel concluded that based on the available data, the safety of CMC as an ingredient in food supplements has not been established. This conclusion was based on the considerations that (i) a provided rat study on the absorption and distribution of 14C-labelled cetylated fatty acids (CFA) had limitations in the design and the test substance used with respect to the proposed novel food ingredient, that (ii) no information was provided on the extent of intestinal hydrolysis of the CFA after oral intake, that (iii) limited information was provided on the distribution of absorbed unhydrolysed CFA, and that (iv) no information was provided on the metabolism and excretion of such intact CFA. In the absence of appropriate data on absorption, distribution, metabolism and excretion (ADME), the provided toxicological data were considered insufficient. No subchronic oral toxicity study and no chronic toxicity study conducted with cetyl myristoleate or CMC had been provided in the original dossier.

The new 90-day study in mice was claimed by the applicant to have been conducted according to OECD Guideline 408 and following Good Laboratory Practice (GLP) conditions. Groups of ten male and ten female Swiss albino mice were administered CMC by gavage daily at the doses of 100 mg/kg, 300 mg/kg and 1000 mg/kg bw for 90 days. The concurrent control group received the vehicle (distilled water) only at 10 ml/kg bw. Additionally, satellite groups of ten mice per sex receiving the vehicle at 10 ml/kg and the test article at 1 000 mg/kg levels were further observed for a period of 28 days following 90 day exposure, for assessment of reversibility, persistence or delayed occurrence of toxicity. The applicant notes that the results of the 90-day study indicate that CMC had no adverse effects on general health, growth, behavioural, neurological, haematological, clinical chemistry and urinalysis parameters, organ weights and gross findings and histo-pathological alterations in mice treated with up to 1000 mg/kg body weight, the highest dose tested. Based on the findings of the 90-day study, the applicant considers that the no observed adverse effect level (NOAEL) of CMC in mice, following oral administration, was 1000 mg/kg body weight, the highest dose tested.

However, the Panel considers that the study and the study report suffer from many shortcomings. EFSA has requested the applicant to address these shortcomings. Some of the issues could satisfactorily be clarified by the applicant. However, several limitations remained after consultation of the applicant: Prior to administration by gavage, doses of CMC in distilled water were prepared fresh each day but actual levels of the test substance in the suspensions were not confirmed analytically; Actual recording of absence of clinical abnormalities did not take place, and clinical observations which were seen in both controls and dose groups were not recorded either; As far as concerns histopathology, the applicant indicates that "all tissues mentioned in OECD 408 were screened for abnormalities, if any", and that "the tissues showing histological findings were recorded", but it is not clear which tissues were examined microscopically; Moreover, the applicant indicates that "normal histological appearances [were] not recorded"; Statistical analyses seem only to have been done on body weight and clinical chemistry, and the lack of any reported statistically significant difference in any parameter is rather unusual for a 90-day study. The Panel also notes the unusually straight line of increases in body weight, and the fact that the strain of mice used was only specified as "Swiss albino mice".

Apart from information on the safety of the hydrolysis moieties and in the absence of sufficient data with respect to kinetics of hydrolysis, adequate safety information on the parent compound CMC remains relevant. The Panel considers that the new 90-day study and its study report have many shortcomings and cannot serve as a reliable source of information supporting the absence of adverse effects of CMC.

The Panel concludes that the safety of 'Cetyl Myristoleate Complex' has not been established.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

On 9 July 2010, EFSA adopted a Scientific Opinion on the safety of 'Cetyl Myristoleate Complex' as a food ingredient (EFSA, 2010).

The conclusion of the EFSA opinion was that, based on the existing data, the safety of Cetyl Myristoleate Complex has not been established. The applicant has now provided additional information, in particular a study report "Repeated Dose 90 day Oral Toxicity Study with 28 Day Recovery Period or Celylated Fatty Acid Esters Powder 50 % in Mice". The applicant is asking to assess the safety of Cetyl Myristoleate Complex in food supplements.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In view of the above, the Commission requests EFSA to review and update its opinion in the light of the additional information.

ASSESSMENT

1. INTRODUCTION

In 2009, the European Commission asked EFSA to carry out an assessment of the safety of 'Cetyl Myristoleate Complex (CMC)' with an intended daily intake of 3.3 g per person per day in the context of Regulation (EC) No 258/97. In 2010, the Panel concluded that based on the available data, the safety of CMC has not been established (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2010).

This conclusion was based on the considerations that (i) a provided rat study on the absorption and distribution of ^{14}C-labelled cetylated fatty acids (CFA) had limitations in the design and the test substance used with respect to the proposed novel food ingredient, that (ii) no information was provided on the extent of intestinal hydrolysis of the CFA after oral intake, that (iii) limited information was provided on the distribution of absorbed unhydrolysed CFA and that (iv) no information was provided on the metabolism and excretion of such intact CFA. In the absence of appropriate data on absorption, distribution, metabolism and excretion (ADME), the provided toxicological data were considered insufficient. No subchronic oral toxicity study and no chronic toxicity study conducted with cetyl myristoleate or CMC had been provided in the original dossier.

'Cetyl Myristoleate Complex' consists of 50 % cetylated fatty acids, 48 % corn starch and 2 % silicon dioxide. The applicant proposed a daily intake of 3.3 g CMC (1.65 g CFAs) which contains approximately 660 mg of both cetyl myristoleate and cetyl myristate, the two main compounds of CMC.

2. ADDITIONAL INFORMATION PROVIDED

In response to the considerations expressed by EFSA in 2010, the applicant provided a new subchronic oral 90-day toxicity study conducted with "Cetylated Fatty Acid Esters Powder 50 %" (Cetyl Myristoleate Complex, CMC) in mice (CMC Study Report, 2012).

This 90-day study in mice was claimed by the applicant to have been conducted according to OECD Guideline 408 and following GLP conditions. However, the Panel notes that the study was not audited independently and that the test facility was not GLP certified. Groups of ten male and ten female Swiss albino mice were administered CMC by gavage daily at the doses of 100 mg/kg, 300 mg/kg and 1000 mg/kg body weight for 90 days. The concurrent control group received the vehicle (distilled water) only at 10 ml/kg. Additionally, satellite groups of ten mice per sex receiving the vehicle at 10 ml/kg and the test article at 1000 mg/kg levels were further observed for a period of 28 days following 90 day exposure, for assessment of reversibility, persistence or delayed occurrence of toxicity.

Daily oral administration of CMC at dose levels of 100, 300 and 1 000 mg/kg bw to groups of ten Swiss albino mice per sex for 90 days was reported not to cause effects on: treatment related mortality, abnormal clinical signs, neurotoxicity, body weights, weekly food consumption, absolute and relative organ weights, haematological parameters, biochemical parameters, urinalysis parameters, gross findings and histo-pathological alterations in the tissues. The applicant notes that the results of the 90-day study indicate that CMC had no adverse effects in mice treated with up to 1 000 mg/kg bw, the highest dose tested.

However, the Panel considers that the study and the study report suffer from many shortcomings. EFSA has requested the applicant to address these shortcomings. Some of the issues could satisfactorily be clarified by the applicant. However, several limitations remained after consultation of the applicant: Prior to administration by gavage, doses of CMC in distilled water were prepared fresh each day but actual levels of the test substance in the suspensions were not confirmed analytically; Actual recording of absence of clinical abnormalities did not take place, and clinical observations which were seen in both controls and dose groups were not recorded either; As far as concerns

histopathology, the applicant indicates that "all tissues mentioned in OECD 408 were screened for abnormalities, if any", and that "the tissues showing histological findings were recorded", but it is not clear which tissues were examined microscopically; Moreover, the applicant indicates that "normal histological appearances [were] not recorded"; Statistical analyses seem only to have been done on body weight and clinical chemistry, and the lack of any reported statistically significant difference in any parameter is rather unusual for a 90-day study. The Panel also notes the unusually straight line of increases in body weight, and the fact that the strain of mice used was only specified as "Swiss albino mice".

DISCUSSION

In the previous Opinion on CMC it was concluded that the information available at that time was not sufficient to establish that the majority of the CFA is hydrolyzed with a kinetic comparable to shorter and longer fatty acid esters (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2010). It was also noted that short linear-chain aliphatic saturated primary esters with an alkyl chain length of up to C_7 would undergo hydrolysis to yield their corresponding linear-chain aliphatic alcohols and linear carboxylic acids, and that any remaining non-hydrolysed esters are expected to be absorbed rapidly from the gastrointestinal tract as well, after which they are also expected to be hydrolysed (EFSA, 2008). As concerns long-chain fatty alcohols esterified to long-chain fatty acids, EFSA noted that there is some information that long chain fatty acid esters are hydrolysed but at a slow rate (EFSA, 2008; EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2010).

Cetylated fatty acids remain intact in the gastro-intestinal tract or are partically or completely hydrolysed into cetyl alcohol (1-hexadecanol) and the fatty acids to which cetyl alcohol is esterified. In the event that all of the CFA would be hydrolysed, the potential adverse effects of CMC would be related to the two hydrolysis moieties: fatty acids and cetyl alcohol. The Panel considers that the fatty acid moieties of CFA do not raise safety concerns as fatty acids are normal constituents of the diet and human body. Hence the potential adverse effects of the hydrolysis products of CFA relate to the cetyl alcohol which accounts for grossly half of the proposed CFA intake corresponding to approximately 12 mg/kg bw. Human health risk assessment of long chain alcohols, including cetyl alcohol (OECD, 2006; Veenstra et al., 2009). It was concluded that the NOAEL in repeated dose toxicity studies (28 day, 13-week and reproduction toxicity tests) were all in a similar range, with the lowest value at 750 mg/kg bw based on cetyl alcohol as the representative linear aliphatic alcohol (Veenstra et al., 2009).

Apart from information on the safety of the hydrolysis moieties, and in the absence of sufficient data with respect to kinetics of hydrolysis, adequate safety information on the parent compound CMC remains relevant. The Panel considers that the new 90-day study and its study report have many shortcomings and cannot serve as a reliable source of information supporting the absence of adverse effects of CMC.

CONCLUSION

The Panel concludes that the safety of 'Cetyl Myristoleate Complex' has not been established.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier consisting of: a) Study Report "Repeated Dose 90 day Oral Toxicity Study with 28 Day Recovery Period of Cetylated Fatty Acid Esters Powder 50% in Mice", Sponsor: EHP Products, P OBox. 2027 Mt. Pleasant, SC 29465, Testing facility TOXINDIA, Plot No. 52, Nilesh Park, Mahesh Soc., Bibwewadi, Pune - 411037, (INDIA).Report: R1140402/S0M·90/11, dated 10 January, 2012, 122 pp and b) File called "2012-03-09 add info introduction.doc", author: Dal Maso, dated 12 March, 2012. Additional information from the applicant was submitted on 15 January and 18 March 2013.

2. Letter from the European Commission to the European Food Safety Authority with the request to review the opinion on the safety of 'Cetyl myristoleate complex' Ref. Ares(2012)700835 - 12/06/2012 received on 12 June 2012.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism and excretion
Bw	Body weight
CFA(s)	Cetylated fatty acid(s)
CMC	Cetyl Myristoleate Complex
GLP	Good Laboratory Practice
NF(I)	Novel food (ingredient)
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development