

Opinion on Diacetyltartaric Acid Esters of Mono- and Diglycerides (Datem E 472e) (expressed on 13 June 1997)

Terms of Reference

To re-evaluate the use of DATEM (E 472e) for general food uses and to consider the use of DATEM (E 472e) in foods for special medical purposes (FSMPs) for infants and young children based on protein hydrolysates and amino-acids, and in infant formulae and follow-on formulae based on partial protein hydrolysates and amino acids for infants in good health.

Background

An application was received in 1992 for the use of E 472e as an emulsifier in mother's milk substitute preparations suitable for infants allergic to cow's milk and/or soya protein and also in FSMPs in children suffering from various metabolic disorders. The Committee has been informed that E 472e is the only technologically useful emulsifier in preparations which do not contain any protein. Clinical information additional to the other data already available in 1974 has now been submitted to the Committee.

This emulsifier was also evaluated by JECFA in 1966 and 1974 (1). In 1966 JECFA established for E 472e an ADI with an unconditional zone of acceptance of 0-25 mg/kg b.w. and a conditional zone of acceptance of 25-50 mg/kg b.w. separately from the ADI for other tartaric esters of mono- and diglycerides because diacetyltartaric acid does not occur in nature. In 1974 JECFA confirmed an ADI of 0-50 mg/kg b.w. for E 472e on the basis of then available data (2). In 1978 the SCF reviewed these data and confirmed an ADI of 0-50 mg/kg b.w. in its First Report on Emulsifiers (3).

The SCF agreed at its 107th Meeting (13th June 1997) to the temporary use of E 472e for 2 years in FSMPs for Infants and Young Children at levels up to 0.3 g/l (as reconstituted from dry powders), up to 0.4 g/l (liquids) and up to 5 g/kg in gluten free bakery products for gluten sensitive patients (4).

Specification

The recent submission contains only the JECFA specification of 1978 (5) for E 472e and quotes a saponification value of 490-520, an acid value of 80-100 and an iodine value of approximately 40. There exists however a new JECFA specification of 1995 (6) which is, however, not mentioned in the new submission.

Evaluation

When the Committee first assessed the safety to health of E 472e it considered only its use as an emulsifier in food generally. A re-evaluation of the available safety data has become necessary, because requests have now been received for the additional use of E 472e in FSMPs for infants and young children and in infant formulae and follow-on formulae for children in good health.

1. Biological data

No biological data additional to those evaluated by the Committee in its First Report on Emulsifiers (3) have presently been submitted to the Committee for evaluation except for some recent clinical studies with a mother's milk substitute containing E 472e. The Committee is also aware, that a long-term study has recently been completed. The original

biological data included a metabolism study in rats fed E 472e labelled with ^{14}C in the 2 carboxyl groups to determine absorption, distribution and excretion through the lungs and in the urine (8). A 22 months feeding study in dogs was used to determine digestibility and the body distribution of the tartaric acid moiety (8). *In vitro* studies demonstrated hydrolysis of E 472e in aqueous media into mono- and di-glycerides, acetylated tartaric acid, acetic acid and tartaric acid, particularly in the presence of pancreatic enzymes (9).

The toxicological data examined in the earlier review included acute toxicity studies in rats, rabbits and dogs. These showed absence of any significant acute toxic effects (8). A 30-day study in dogs given E 472e i.v. and a feeding study in dogs extending over 25½ months, also showed no adverse effects even at the 20% dose level in the feed (10). In a 2 year feeding study in rats, no adverse effects attributable to E 472e even at 20 % incorporation in the diet, the highest dose level tested, were noted (8). Furthermore, a reproduction study in rats extending over 22 months also showed no adverse findings related to the feeding of E 472e up to a dose level of 20 % in the diet (8). E 472e was found to be non-mutagenic in *in vitro* assays using *Salmonella typhimurium* and *Saccharomyces cerevisiae*. (14)

2. Human clinical data

Several recent tolerance trials with a mother's milk substitute preparation containing 2000 mg/kg E 472e were carried out in new-born infants at high risk for atopy and in infants and children known to suffer from allergy to cow's milk. The parameters examined included weight gain, growth, titre of IgE specific for cow's milk, incidence of positive skin prick tests for allergy to cow's milk and incidence of allergy to cow's milk. In none of these prospective studies were any adverse effects noted in the parameters examined other than those due to the existing underlying allergy or atopic predisposition (11,12,13).

Predicted intakes

Given the requested levels of use of E 472e in foods for infants and their low body weights, it is relevant to compare the predicted intakes with the ADI for E 472e of 50 mg/kg b.w. and the possible formation of one of its hydrolysis products, tartaric acid, with the ADI for that substance of 30 mg/kg b.w.

The requested levels of use of E 472e in formulae and follow-on formulae based on hydrolysed proteins for infants in good health and for use in FSMPs vary considerably. One group of products requires levels up to 0.175g/100g of dry product, while others require 1.2-3g/100g of dry product (15). Intake data have been provided for 3 typical products in the lower use range of E 472e and these all give estimated intakes of E 472e which are at or below an ADI of 50 mg/kg b.w. (16). Intake data have also been provided for a typical product in the upper use range of E 472e, containing 1.6g/100g of dry product. These intake data range from 194-274 mg/kg b.w./day for infants between 0-12 months of age (15), implying they would regularly exceed the ADI.

Considering tartaric acid, the Committee has been informed that the E 472e preparations requested for use in formulae and follow-on formulae based on hydrolysed proteins for infants in good health and for use in FSMPs would conform to Food Chemical Codex limits, i.e., would contain up to 20% tartaric acid (15). Thus any intake of more than 150 mg/kg b.w./day of this type of E 472e preparation could exceed the ADI for tartaric acid. This suggests that use of E 472e at the requested higher use range of 1.2-3g/100g of dry product would result in the ADI for tartaric acid being regularly exceeded. (It should also be noted that the EU specification for E 472e allows preparations containing up to 40% tartaric acid to be used in the European Community).

Conclusions

The Committee has reviewed the total information on E 472e presently available to it and has noted that a new specification for E 472e, aligned with the one of 1995 has not been supplied. The biological data show that hydrolysis in the mammalian gut is sufficiently slow to allow the absorption of some unhydrolysed E 472e. The identity of the urinary metabolite remains undetermined. The compound has no acute toxicity by the oral route. The available short-term, long-term and reproduction studies, though inadequate by present-day standards, provide collateral evidence for

the absence of serious adverse effects, when E 472e is ingested in high doses. Genotoxicity has not been adequately studied as neither *in vitro* nor *in vivo* tests for chromosomal aberrations have been provided. However, the clinical studies with a mother's milk substitute containing E 472e demonstrate that E 472e is well tolerated by infants and children suffering from allergy to cow's milk.

In these circumstances the Committee is presently prepared to set a temporary ADI of 25 mg/kg b.w. for general food uses which represents half the ADI established in 1978, but wishes to see the full presentation of the recently completed long-term feeding study in laboratory animals within 3 months. In the absence of these data the Committee may have to consider further restrictions on the use of E 472e.

The Committee is unable to express a view on whether E 472e is acceptable for use in formulae and in follow-on formulae based on hydrolysed proteins for infants in good health and in the meantime considers that it should not be used in such products. As mentioned previously, the Committee has already agreed to the temporary use of E 472e for two years in FSMPs.

The Committee will reconsider the request for use in infant formulae and in follow-on formulae based on hydrolysed proteins for infants in good health, its recent temporary acceptance for use in FSMPs and the temporary ADI now set for general food use once the following information is supplied, or within two years of publication of this opinion, whichever is the earlier:

1. An adequate specification which also includes a limitation for tartaric acid to 20%
2. Full submission of the recently completed long-term study in laboratory animals
3. Studies on reproduction and teratology conducted to modern standards
4. A test for chromosomal aberrations in mammalian cells *in vitro*

References

1. JECFA (1974) Toxicological evaluations published in WHO Techn. Rep. Ser. No 539
2. WHO (1974) WHO Food Additives Series No.5, 222-224
3. SCF (1978) Seventh Series of Reports, 10.
4. SCF (1997) Minutes of 107th Meeting, Item 4.2
5. FAO/WHO (1978) Specifications listed in FNP 4,257
6. FAO/WHO (1995).Specification listed in FNP 52 Add 3/61
7. Lang,K. & Schmidt,D. (1965) Unpubl. Report submitted to WHO.
8. Koppanyi,T. & Dardin,V. (1950) Unpubl. Report submitted to WHO.
9. Sourkes,T.L. & Koppanyi,T. (1950) J.Amer.Pharm.Assoc.,Sci.Ed., 39, 275.
10. Hartwig,Q.L., Singleton,W.S. & Collar,A.M. (1962) Toxicol.Appl.Pharmacol., 4, 107-115.
11. Halken,S., Host,A., Hansen,L.G. & Osterballe,O. (1992) Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. *Allergy*, 47, 545-553.
12. Halken,S., Host,A., Hansen,L.G. & Osterballe,O. (1993) Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study. *Pediatr.Allergy.Immunol.*, 4, 173-181.
13. Halken,S., Host,A. Hansen,L.G. & Osterballe,O. (1993) Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. *Pediatr. Allergy.Immunol.*, 4, 53-59
14. FDA (1976) Mutagenic Evaluation of Compound FDA 75-31, 977051-29-8 Monoglyceride Diacetyltartaric Acid Ester, Litton Bionetics, Kensington,Md. in National Technical Information Service, PB-280 111.
15. IDACE (1996) DATEM E 472e (Diacetyltartaric acid esters of mono- and diglycerides) CS/ADD/MsAd/152, October 1996. Unpublished submission to the Scientific Committee for food by IDACE, Paris.
16. IDACE (1995) Requests and supporting technological justifications for amendments to the European Parliament and Council Directive 95/2/EC of 20 February 1995 on Food Additives Other Than Colours And Sweeteners. CS/ADD/MsAd/126, May 1995. Unpublished submission to the Scientific Committee for Food by IDACE, Paris.