CODEX ALIMENTARIUS COMMISSION E

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World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FOOD ADDITIVES

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DISCUSSION PAPER ON FOOD ADDITIVE PROVISIONS IN THE *STANDARD FOR INFANT FORMULAS AND FORMULA FOR SPECIAL MEDICAL PURPOSES* (CODEX STAN 72-1981)

Prepared by Switzerland

1. This Discussion Paper was prepared by the delegation of Switzerland as a follow up to the 42nd session of the Codex Committee on Food Additives (CCFA) (paragraphs 168-169 of ALINORM 10/33/12). Indeed, the Committee noted that the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) was still waiting for advice on a number of food additive provisions forwarded by its 28th session to the CCFA.

Background & history

2. When revising the Codex Standard for Infant Formula and Formulas for Special Medical Purposes (CODEX STAN 72-1981), the CCNFSDU received proposals for a considerable number of food additives which had not been included previously in *Section 4 Food additives* of the standard.

3. Diverging opinions about the use of food additives in infant formula were aired during the 28th session of the CCNFSDU in 2006 (paragraphs 57 – 68 of ALINORM 07/30/26-Rev.); the discussion focused on the criteria for the use of additives in infant formula. The Committee agreed to put forward to CCFA three more fundamental questions on this matter (paragraph 58):

a. To what extent an ADI established by JECFA, whether numerical or not specified, applied to young infants below 12 weeks;

b. What scientific principles should apply to the evaluation of additives intended for this group of population; and

c. Whether the establishment of an ADI in itself was sufficient or whether other issues had to be addressed.

4. In accordance with the Procedural Manual, the CCNFSDU forwarded the food additives that have been listed for many years in CODEX STAN 72-1981 to CCFA for endorsement (paragraph 66 of ALINORM 07/30/26-Rev).

5. The lists of the remaining new additives that had been proposed for inclusion in the standard were sent to CCFA for advice as regards their suitability in *Infant formulae* (Section A of the standard) and *Formulas for Special Medical Purposes Intended for Infants* (Section B). It was expected by CCNFSDU that such substance-specific advice would reflect the advice on the general questions (see 3) and state whether an evaluation of the additives by JECFA was required (paragraph 67 of ALINORM 07/30/26-Rev).

6. In response to the requests from CCNSFDU the 39th session of CCFA endorsed (with few exceptions) in 2007 the additives that had been listed in the existing version of CODEX STAN 72-1981 for several years (paragraphs 57 – 61 of ALINORM 07/30/12 Rev).

7. The questions from CCNSFDU and the new proposed additives were discussed briefly and the Committee agreed to consult JECFA on the questions raised by the CCNFSDU and to consider the new

additives once the general advice from JECFA became available (paragraph 29 and Appendix XV of ALINORM 07/30/12 Rev).

8. At its 29th session in 2007, the CCNSFDU took note of the clarification provided by the JECFA Secretariat regarding the applicability of the ADI concept for infants below 12 weeks of age and agreed that there was no need to consider the food additives provisions at the Committee before JECFA and CCFA concluded their work on remaining food additive issues posed by the 28th Session of the Committee (paragraph 15 of ALINORM 08/31/26).

9. At its 40th session in 2008, the CCFA asked the In-session Working Group on Priorities for Evaluation by JECFA to consider the matter and followed the Working Group's proposal to provide an official reply to CCNFDSU (paragraph 171 and Appendix XV of ALINORM 08/31/12).

10. This reply from ALINORM 08/31/12 is attached as Annex I to this Discussion paper and the three questions were answered in it by CCFA as follows (excerpts of the relevant sentences from the reply arranged according to the questions):

a. To what extent an ADI established by JECFA, whether numerical or not specified, applied to young infants below 12 weeks?

Reply

[...] for most food additives the ADIs allocated are applicable only to children older than 12 weeks. Food additives should not generally be used in foods for infants and very young children. JECFA is continuing to maintain this general position to date. [...]

Certain food additives have been evaluated for safety of use in infant formula on a case-by-case basis.

b. What scientific principles should apply to the evaluation of additives intended for this group of population?

Reply

Specific data to demonstrate safety for this age group are required, and this depends on the toxicological profile and potential concern for the compound. Consequently, the existence or establishment of an ADI based on standard toxicological data packages is not sufficient. [...]

Since the usual protocols for toxicological studies do not directly cover the developmental period in question, specific guidance for toxicological testing for substances likely to be used in infant foods is given [by EHC 70].

c. Whether the establishment of an ADI in itself was sufficient or whether other issues had to be addressed?

Reply

[...] the existence or establishment of an ADI based on standard toxicological data packages is not sufficient. [...] Specific data to demonstrate safety for this age group are required

Currently valid principles

11. The above mentioned principles were developed forty years ago based on the advice of an FAO/WHO meeting on additives in baby food held in 1971 and subsequent additional considerations by JECFA. The recently published FAO/WHO guidance on the *Principles and methods for the risk assessment of chemicals in food* reinforced them in the subchapter *Subpopulations at risk* on pages 7-17/7-18:

> *"Very young infants are a particularly sensitive subgroup because their metabolic capacities are not yet fully developed. It should be noted that health-based guidance values are not considered applicable to infants under the age of 12 weeks who might be at risk at lower levels of exposure. Accordingly, risk characterization of exposure of such infants to chemicals (e.g. in infant formula or occurring as contaminants) has to be considered on a case-by-case basis. This is in accordance with similar advice in EHC 70 (IPCS, 1987), where the scientific rationale for this conclusion was originally set out. EHC 237, which provides a systematic analysis of the scientific principles to be*

considered in assessing health risks in children from exposures to environmental agents during distinct stages of development, is a useful reference in this regard (IPCS, 2006)." [1]

12. The guidance provided by EHC 70 is worthwhile to be repeated because it outlines the expectations of experts towards a toxicological database that should be available if a food additive was to be used in foods for very young infants:

"[…] guidelines on toxicological testing include the following:

(a) Before a food additive is regarded as safe for use in food intended for infants up to 12 weeks of age, the toxicological studies should be extended to include animals in the corresponding period of life.

(b) It is difficult to recommend precise toxicological testing procedures until more basic research has been undertaken. There are also difficulties in selecting appropriate species. In these circumstances, short- term studies should be conducted in several species and should include the oral administration of the additive under test, at suitable dose levels, to newly born animals up to and including the end of the weaning period.

(d) When life-span studies and multi-generation studies are carried out, they should be extended to include oral administration of the food additive at suitable dose levels to a proportion of animals from the day of birth throughout the pre-weaning period.

The practical difficulties and cost of implementing these recommendations on a routine basis would be immense, involving, as it would, artificial feeding of litters of newborn laboratory animals. However, in situations in which young infants are a target population for an additive, it seems reasonable that studies such as these should be performed."

13. In short, the toxicological database for a food additive needs to provide data from studies where animals of a comparable life stage have been exposed to the chemical in question and such data need to provide reasonable evidence that the substance would cause no harm in infants below 12 weeks of age. The assessment of substances cannot be done using a schematic approach but rather case-by-case taking into account separately the data available for each substance.

Characterization of requested additives

14. Based on the summary provided in paragraphs 11-13 there is no simple answer to CCNFSDU. The requested additives (see Annex II) are a mixed bag of substances with different profiles. However, these additives were not forwarded to the CCFA for endorsement and therefore CCFA will not take any position whether their eventual use in infant formula is acceptable. The following considerations are offered in order to facilitate the discussion:

15. Some additives may be considered physiological body constituents such as the salts of citric or phosphoric acids which consist of ions such as calcium, sodium, citrate, phosphate that are part of additives already permitted by the standard or of minerals listed in the *Advisory List of Mineral Salts and Trace Elements for Use in Foods for Special Dietary Uses Intended for Infants and Young Children* (CAC/GL 10-1979). Should the CCNFSDU propose those for inclusion in Section A of the standard, CCFA may consider endorsing their use provided that levels of potassium, sodium and phosphorus in the formula are compatible with the nutritional requirements of infants.

16. Other proposed additives are - in adults - physiological metabolites of compounds that occur also in food. Mono- and diglycerides e.g. may already be present in raw materials used in the manufacturing of formulae; however, an increase of their level may require an assessment whether such levels pose a hazard to the incompletely developed gastric tract of infants.

17. Several substances, among them specifically the proposed thickeners and emulsifiers are xenobiotics for which an assessment from JECFA is available but an adequate database would be required along the lines summarized above before they would be acceptable for use in infant formula.

18. The three proposed antioxidants (E306, E308, E309) are substances that have not yet been assessed by JECFA at all and a more comprehensive full assessment would be required before considering their use as food additives.

[1] http://www.who.int/ipcs/food/principles/en/index1.html

The current Codex framework

19. The current restricted list of additives permitted in infant formula and similar products intended for very young infants (< 12 weeks of age) results from a policy recommended by the FAO/WHO Meeting on Additives in Baby Food in 1971. The meeting's report was considered by JECFA, modified and subsequently adopted by the Committee as guidance[2]. The introduction stated:

> *Baby foods should be prepared without food additives whenever possible. Where the use of a food additive becomes necessary in baby foods, great caution should be exercised regarding both the choice of additive and its level of use.*

20. This policy was implemented subsequently by the CCFA at its 9th session (ALINORM 74/12) and the CCFNDSU at its 8th session (ALINORM 76/26).

21. Both committees, the CCFA and the CCNFSDU, may wish to consider whether the principle should be maintained that the use of food additives baby foods and specifically in infant formulae should be restricted as much as possible.

22. This policy did not consider specifically formulas for special medical purposes intended for infants, a food category which may be different from infant formula with respect to the risk/benefit balance. CCFA and CCNFSDU may wish to consider whether a different policy for these formulas with respect to using food additives is warranted.

23. The use of food additives in infant formula requires an assessment whether the likely exposure will constitute an unacceptable risk for infants. It should be based on an evaluation by JECFA (or another expert opinion of an equivalent reputation provided by FAO/WHO).

24. Requests for such assessments should follow the existing policies and procedures laid down in the *Procedural Manual* and the working arrangements as agreed between CCFA and JECFA. Any proposal for an assessment of an additive by JECFA needs to be presented to the CCFA using the form circulated together with the circular letter that asks for proposals for the priority list of substances to be evaluated by JECFA. When providing information about the available data the sponsor should emphasize what data are available that would allow an assessment of the additive's safety for infants below twelve weeks of age. The in-session Working Group on Priorities for Evaluation by JECFA will examine the proposal and may - if the data requirements are met – include it into the priority list of JECFA.

Recommendations

25. **The Committee is invited to consider the following recommendations**:

26. **Recommendation I**: The Committee agrees that the principle that was discussed and proposed by JECFA in 1971 and subsequently implemented by the Codex Alimentarius Commission when adopting standards for baby food remains valid:

> *"Baby foods should be prepared without food additives whenever possible. Where the use of a food additive becomes necessary in baby foods, great caution should be exercised regarding both the choice of additive and its level of use. (Annex 3 of TRS 488)."*

27. **Recommendation II**: Proposals for the inclusion of an additive in Codex standards for foods intended for infants below 12 weeks of age require a separate evaluation by JECFA since for additives used in food for this population the toxicological investigations should be more extensive and include evidence of safety to young animals. Requests for evaluation should be presented to the CCFA. Such requests should be made using the agreed form, include an inventory of available studies and should state that the data meet the requirements for this age group by JECFA as laid down in the *Principles and methods for the risk assessment of chemicals in food* (EHC 240) and the *Principles for the safety assessment of food additives and contaminants in food* (EHC 70).

28. **Recommendation III**: The CCNFSDU is invited to consider this discussion paper and both recommendations and to provide feedback to the CCFA and, if deemed necessary, make proposals for further discussions and amendments to the currently applied approach by Codex.

[2] Report available as Annex 3 of the report from the 15th meeting of JECFA (TRS 488).

Annex I

ALINORM 08/31/12, Appendix XV

CCFA RESPONSE TO THE CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES ON THE APPLICABILITY OF ADIs TO INFANTS AND YOUNG CHILDREN

In response to the following request by CCNFSDU, the JECFA Secretariat would like to provide the following response:

To what extent does an ADI established by JECFA, whether numerical or not specified, apply to young infants below 12 weeks; what scientific principles should apply to the evaluation of additives intended for this group of population? Is the establishment of an ADI in itself sufficient or do other issues need to be addressed?

JECFA has considered this specific question on several occasions. In particular at its twenty-first meeting, and a detailed consideration of this issue is published in the report[3]. The Committee at that time concluded that for most food additives the ADIs allocated are applicable only to children older than 12 weeks. The Committee also pointed out that food additives should not generally be used in foods for infants and very young children. JECFA is continuing to maintain this general position to date.

More detailed guidance on this matter is contained in EHC 70: Principles for the safety assessment of food additives and contaminants in food, published in 1987[4]. These principles are based on the advice of an FAO/WHO meeting on additives in baby food held in 1971 and additional considerations by JECFA subsequently. Since the usual protocols for toxicological studies do not directly cover the developmental period in question, specific guidance for toxicological testing for substances likely to be used in infant foods is given.

Certain food additives have been evaluated for safety of use in infant formula on a case-by-case basis. Specific data to demonstrate safety for this age group are required, and this depends on the toxicological profile and potential concern for the compound. Consequently, the existence or establishment of an ADI based on standard toxicological data packages is not sufficient.

These basic principles are still valid to date, however in light of advancing science it may be appropriate to perform a detailed scientific review and give further guidance on this matter. A recent WHO publication[5] details some biological and scientific principles on the susceptibility of children and may serve as a starting point for the development of further applied guidance on the applicability of health-based guidance values, like ADIs and TDIs, to infants and young children, including data requirements for safety assessment for these age-groups. Initial discussions to elaborate such an activity have commenced at WHO, but no time-lines have been set.

[3] WHO Technical Report Series 617: Evaluation of certain food additives, WHO Geneva 1978.
[4] Environmental Health Criteria 70: Principles for the safety assessment of food additives and contaminants in food. WHO, Geneva 1987.
[5] Environmental Health Criteria 237: Principles for evaluating health risks in children associated with exposure to chemicals. WHO, Geneva 2006.

Annex II

Request for additional food additives for use in infant formula (Section A) and formula for specific medical purposes (Section B) *(from TABLE 2: ALINORM 07/30/26-Rev., APPENDIX III)*

INS no.	Additive	Maximum level in 100 ml of the product ready for consumption	Technological Justification
4.1 Thickeners			
415	Xanthan gum	GMP	Retains homogeneity
414	Gum arabic (acacia)	GMP	Retains homogeneity
4.2 Emulsifiers			
472c	Citric and fatty acid esters of glycerol	0.75 g in powder formula[1)] 0.9 g in liquid formula containing hydrolysed protein or amino acids[1)]	Retains homogeneity
473	Sucrose esters of fatty acids	12 mg in formula containing hydrolysed protein or amino acids[1)]	Retains homogeneity
472e	Tartaric and fatty acid esters of glycerol	0.5 mg	Retains homogeneity
472a	Acetic and fatty acid esters of glycerols	GMP	Retains homogeneity

[1)] If more than one of the substances INS 472c, 473 are added the maximum level for each of those substances is lowered with the relative part as present of the other substances

INS no.	Additive	Maximum level in 100 ml of the product ready for consumption	Technological Justification
4.3 Acidity Regulators			
331i	Sodium dihydrogen citrate	0.2 g singly or in combination and within the limits for sodium, potassium and calcium in section 3.1.3 (e) in all types of infant formula	pH adjustment
331iii	Trisodium citrate		pH adjustment
332i	Potassium dihydrogen citrate		pH adjustment
332ii	Tripotassium citrate		pH adjustment
338	Phosphoric acid	0.1 g expressed as P_20_5 singly or in combination and within the limits for sodium, potassium and phosphorus in section 3.1.3(e) in all types of infant formula	pH adjustment
339i	Monosodium dihydrogen monophosphate		pH adjustment
339ii	Disodium hydrogen monophosphate		pH adjustment
339iii	Trisodium monophosphate		pH adjustment
340i	Monopotassium dihydrogen monophosphate		pH adjustment
340ii	Dipotassium hydrogen monophosphate		pH adjustment
340iii	Tripotassium monophosphate		pH adjustment
4.4 Antioxidants			
306	Vitamin E concentrate	1 mg in all types of infant formula singly or in combination	Protects from oxidation
309	Gamma-tocopherol		Protects from oxidation

INS no.	Additive	Maximum level in 100 ml of the product ready for consumption	Technological Justification
308	Delta-tocopherol		Protects from oxidation

Request for additional food additives for use in formula for specific medical purposes (Section B)
(from TABLE 2: ALINORM 07/30/26-Rev., APPENDIX III)

INS no.	Additive	Maximum level in 100 ml of the product ready for consumption	Technological Justification
4.1 Thickeners			
401	Sodium alginate	100 mg	Retains homogeneity
405	Propane 1,2-diolalginate	20 mg	Retains homogeneity
410	Carob bean gum (Locust bean gum)	0.5 g	Retains homogeneity
412	Guar gum	1 g	Retains homogeneity
415	Xanthan gum	0.12 g	Retains homogeneity
440	Pectins	1 g	Retains homogeneity
466	Sodium carboxymethyl cellulose	1 g	Retains homogeneity
1450	Starch sodium octenyl succinate	2 g	Retains homogeneity
414	Gum arabic (acacia)	GMP	Retains homogeneity
4.2 Emulsifiers			
471	Mono- and diglycerides	0.5 g	Retains homogeneity
472c	Citric and fatty acid esters of glycerol	0.75 g in powder formula 0.9 g in liquid formula containing partially hydrolysed protein, peptides or amino acids	Retains homogeneity