COMMENTARY—*Food Chemicals Codex* (*FCC)*
Seventh Edition, First Supplement
August 31, 2010

In accordance with USP's Rules and Procedures of the Council of Experts, USP publishes all proposed revisions to the *Food Chemicals Codex (FCC)* for public review and comment in the *FCC Forum* (*FCCF)*, USP's journal for public notice and comment for *FCC*. After comments are considered and incorporated as the Food Ingredients Expert Committee (FIEC) deems appropriate, the proposal may advance to effective status or be republished in *FCCF* for further notice and comment, in accordance with the Rules and Procedures. In cases when proposals advance to effective status without republication in *FCCF*, a summary of comments received and the FIEC's responses are published in the *Commentary* section of the USP Web site at the time the revision is published.

The *Commentary* section below is not part of the text of the monograph or general test or assay. Rather, it explains the basis of the FIEC's response to public comments. If there is a difference between the content of the *Commentary* section and the monograph or general test or assay, the text of the monograph prevails. In case of a dispute or question of interpretation, the language of the monograph text, alone and independent of the *Commentary* section prevails.

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No comments were received for the following proposals:

General Tests and Assays
Appendix III—Chemical Tests and Determinations
Appendix VII—Fats and Related Substances
Appendix XII—Microbiological Tests

Monographs
4-(P-Hydroxyphenyl)-2-Butanone
5'-Cytidylic Acid
Alpha-Lactalbumin
Ascorbyl Palmitate
Calcium Lignosulfonate (40-65)
Carbon, Activated
Crospovidone
D-Camphor

No comments were received for the following proposals, continued:

Monographs, continued
D-Carvone
D-Dihydrocarvone
D-Fenchone
D-Limonene
Diacetyl Tartaric Acid Esters of Mono- and Diglycerides
Diethyl Sebacate
Disodium 5'-Uridylate
DL-Menthyl Acetate
Ethyl Acetate
Ferric Phosphate
Glyceryl Monooleate
L-Carveol
L-Carvone
L-Carvyl Acetate
L-Limonene
L-Menthone
L-Menthyl Acetate
Nisin A Preparation
Phosphoric Acid
Potassium Phosphate, Dibasic
Potassium Phosphate, Monobasic
Potassium Phosphate, Tribasic
Propylene Oxide
Rebaudioside A
Sodium Phosphate, Monobasic
Tartaric Acid

COMMENTARY— *FCC* Seventh Edition, First Supplement

Monograph/Section(s): 5'-Adenylic Acid; 5'Cytidylic Acid; and Disodium 5'-Uridylate/Multiple
Expert Committee(s): Food Ingredients
No. of Commenters: 3
Comment Summary #1: The commenter indicated that three production methods can be used to produce these nucleotides (degradation of RNA, fermentation, and chemical synthesis), and questioned why the latter two were not included in the scope of this monograph.

Response: Comment not incorporated. The FIEC responded that the monograph was developed on the basis of data submitted for one process method used to produce materials permitted for use in foods. The FIEC encouraged manufacturers to work with USP to refine the scope of these monographs in the future to include all processes and related impurities that represent food-grade materials, and to exclude materials not permitted for use in foods.

Comment Summary #2: The commenter requested spelling out the term RNA in the *Description* as ribonucleic acid (RNA)

Response: Comment incorporated.

Comment Summary #3: The commenter supported use of the proposed infrared test for *Identification*, but requested that the UV tests used in the Australia/New Zealand standards be considered as an additional test.

Response: Comment not incorporated. Data was not supplied to support the use of UV tests for identification.

Comment Summary #4: The commenter requested that the *Assay* acceptance criteria be tightened to NLT 99.5% since the limit for Other Ribonucleotides is NMT 0.5%.

Response: Comment not incorporated. The FIEC responded that the acceptance criteria was developed based on data provided to the FIEC including capability of the HPLC analytical method and batch data for food-grade batches.

Comment Summary #5: The commenter indicated that they produce materials meeting or exceeding the proposed limits for *Inorganic Impurities*, but questioned the basis for the proposed limits and why the Heavy Metals (as Lead) test and specification of NMT 10 mg/kg was not used.

Response: Comment not incorporated. The FIEC responded that *FCC*'s current policy on heavy metal impurities is to test individual metal impurities and to set limits consistent with food safety and as low as practical based on data supplied to the FIEC on manufacturing process capability, good manufacturing practices, and analytical capability (see http://www.usp.org/fcc/fccPolicies.html). FIEC indicated that the proposed limits are consistent with this policy and based on data supplied.

Comment Summary #6: The commenter noted that the three monographs have different limits for *Ethanol* (100, 200, and 1000 mg/kg), and suggested that one limit for ethanol be established for all three nucleotides. The commenter also commented on references the current ICH "Impurities: Guideline for Residual Solvents Q3C(R4)" (http://www.ich.org/LOB/media/MEDIA5254.pdf) (pg 12) that suggests a 5000 mg/kg limit for ethanol is appropriate for pharmaceuticals, and suggested that this limit or 3000 mg/kg be used all three proposed *FCC* monographs.

Response: Comment not incorporated. The FIEC indicated that the limits proposed were based on data supplied to the FIEC for each individual nucleotide

in an effort to limit the level of this impurity to the lowest level considering manufacturing process capability and good manufacturing practices.
Comment Summary #7: The commenter noted that the three proposed monographs have different limits for *Other Ribonucleotides* (0.5, 0.5, and 1%), and suggested that they be set at 0.5%.
Response: Comment not incorporated. The FIEC indicated that the limits proposed were based on data supplied to *FCC* for each individual nucleotide in an effort to limit the level of these impurities to the lowest level considering manufacturing process capability and good manufacturing practices.
Comment Summary #8: The commenter supported the proposed microbial tests and limits, but suggested that tests and limits for coliforms and *E. coli* should be included, the former of which is included in the Australia/New Zealand standards for these three nucleotides.
Response: Comment not incorporated. The FIEC responded that this class of microorganisms is already covered by the proposed monograph under the *Bile-Tolerant Gram-Negative Bacteria* test.
Expert Committee Initiated Change #1: The FIEC removed the terms “natural source” from the *Description* of this ingredient because it is unnecessary.
Expert Committee Initiated Change #2: The FIEC added 0.005 µg/mL and 0.025 µg/mL standard solution concentrations for the *Cadmium* and *Mercury* tests, respectively, so that the sample testing limit is included in the standard curve range. This change was confirmed by data from the monograph sponsor.
Expert Committee Initiated Change #3: For the 5’-Adenylic Acid and 5’Cytidylic Acid monograph proposals, the FIEC changed the note in the sample solution procedure for the *Assay* and *Other Ribonucleotides* tests to include a suitable procedure for preparing these solutions. This was in response to comments received indicating difficulty in preparing 1.0 mg/mL solutions as directed in the proposals due to low solubility of these ingredients. This change was confirmed by data from the monograph sponsor.
Expert Committee Initiated Change #4: The FIEC changed the sample testing concentration and acceptance criteria for *pH* in the 5’-Adenylic Acid and 5’Cytidylic Acid monograph proposals. This was in response to comments received indicating difficulty preparing the proposed 10 mg/mL sample solution. This change was confirmed by data from the monograph sponsor.

Monograph/Section(s): Betaine/Multiple
Expert Committee(s): Food Ingredients
No. of Commenters: 0
Expert Committee Initiated Change #1: The FIEC added an appropriate FEMA number and *Function* of “flavoring agent” to the monograph because this ingredient also is permitted for flavoring use in foods.

Expert Committee Initiated Change #2: The FIEC changed the physicochemical properties listed in the *Description* to reflect the very hygroscopic nature of this food ingredient. This change was confirmed by data from the monograph sponsor.
Expert Committee Initiated Change #3: The FIEC changed the acceptance criteria for *Infrared Absorption* to require the presence of absorbance bands at wavelengths characteristic to betaine and not betaine and water. This was done to ensure that both anhydrous and dehydrate forms of betaine can pass this test. This change was confirmed by data from the monograph sponsor.
Expert Committee Initiated Change #4: The FIEC added a *Note* to the *Assay* indicating the very hygroscopic nature of the ingredient and to emphasize the need for appropriate handling in test procedures.
Expert Committee Initiated Change #5: The FIEC changed the "IU" term in the equation for the *Color* test to the more descriptive term "Color".

Monograph/Section(s): DHA Algal Oil, *Crypthecodinium* Type/Multiple
Expert Committee(s): Food Ingredients
No. of Commenters: 3
Comment Summary #1: The commenter noted inconsistencies in naming the same ingredient in the *FCC* and the *USP-NF* and suggested that the title of the monograph be changed to "DHA Algal Oil (*Crypthecodinium cohnii*)" to reflect the product being sold and the Latin binomial of the source organism.
Response: Comment not incorporated. The FIEC did not want to establish a title that is inconsistent with other ingredients in the *FCC*.
Comment Summary #2: The commenter requested that the minimum amount of DHA in the *Definition* be stated as "mg/g" instead of "w/w" to match current industry practice.
Response: This comment does not apply as *FCC* does not have a *Definition* section and *FCC* does not specify DHA content in the *Description* section.
Comment Summary #3: The commenter requested that the proposed *Identification* test and requirements be removed and replaced with a requirement that the ingredient "is characterized by significant amounts of long-chain C22 fatty acids. The sum of the area peak for DHA methyl esters is not less than 35%." The commenter stated that the current proposed test and specifications under *Identification* are unnecessarily prescriptive and restrictive and that the limits on the other fatty acids that have been proposed have no relevance to the safety or functional properties of the oil, nor do they characterize the oil. The commenter further states that the current proposed specifications provide a commercial advantage to the manufacturer whose product was used as the basis for the limits and that this approach is inconsistent with the approaches taken by regulatory agencies in Australia, Brazil, Canada, China, Europe, Indonesia, and Korea and that it is inconsistent with voluntary guidelines used by industry.

Response: Comment not incorporated. The FIEC considers the fatty acid composition profile proposed in the *Identification* section crucial to proper identification of the ingredient and necessary to differentiate oils from different sources. This approach is used in all other monographs for fats and oils in *FCC* and could potentially be used to determine whether the ingredient is adulterated.

Comment Summary #4: The commenter requested that the specification for the minimum DHA content in the ingredient be changed from "NLT 40.0%" to "NLT 35%" in the *Assay* to ensure consistencies with global approvals.

Response: Comment not incorporated. The commenter did not provide specific batch data to support the requested specification change. The original proposed specification is consistent with publicly available data for the ingredient.

Comment Summary #5: The commenter requested that the unit of measure for inorganic impurities be listed as "mg/kg" to remain consistent with global regulations and industry policy.

Response: Comment not incorporated. The proposed monograph already gives specifications for *Inorganic Impurities* (*Arsenic, Lead,* and *Mercury*) in mg/kg units.

Comment Summary #6: The commenter requested that the *Labeling* requirement be changed to state the content of DHA as a percentage and not as mg/g. The commenter stated that product certificates of analysis already provide customers with information regarding the DHA content in mg/g and that these certificates, and not the product labels, are used by customers to accept product shipments. Furthermore, the commenter believes that a requirement to add the DHA content in mg/g to product labels does not provide a measurable benefit to the integrity of the product and would result in unnecessary customer notifications.

Response: Comment incorporated, with changes. The FIEC had concerns that all users of the monograph will not calculate percent DHA in the same manner (uncorrected to an internal standard or correction factor), which could cause inconsistencies in reporting the content of DHA. For this reason the FIEC changed the *Labeling* such that the label provides the content of docosahexaenoic acid (DHA) in "mg/g (%)."

Comment Summary #7: The commenter requested that the requirement under *Labeling* listing the concentration of added antioxidants on product labels be deleted from the monograph since the products are manufactured according to applicable U.S. and global regulations, which do not require such a quantitative declaration. Furthermore, the commenter noted that the addition of the antioxidant concentration to labels is overly burdensome to manufacturers and does nothing to further ensure the safety or quality of the product.

Response: Comment incorporated.

Comment Summary #8: The commenter requested that the *Function* of the ingredient be changed from "nutrient" to "nutrient ingredient."

Response: Comment not incorporated. The FIEC did not receive justification for this request and noted that *FCC* does not currently use the function "nutrient ingredient" for any other monographs. Furthermore, since the term "nutrient" is ambiguous, the FIEC deleted that term from the *Function*, leaving "Source of DHA" as the *Function* of the ingredient.
Comment Summary #9: The commenter requested that the color of the ingredient from the *Description* be changed from "yellow to orange" to "light yellow to dark orange."
Response: Comment incorporated with changes. The FIEC did not receive justification for this request, but noted that the color of this oil could be lighter than what one might consider yellow. To accommodate lighter-colored oils, the FIEC changed the *Description* to replace "yellow to orange" with "light yellow to orange."
Comment Summary #10: The commenter questioned the need for this monograph and their belief that this ingredient is not widely manufactured. The commenter also questioned whether this monograph is useful to the food industry.
Response: Comment not incorporated. The FIEC believes that the *FCC* should be a source of public standards for commercially-available food ingredients, of which this is one. The FIEC considers a public standard useful to ingredient manufacturers, formulators, food manufacturers, and consumers.
Comment Summary #11: The commenter stated that there is a voluntary industry monograph that was developed in conjunction with manufacturers of DHA products and provided a copy of the specifications required by this monograph. The commenter provided information regarding the group that developed the voluntary monograph and requested that the FIEC review the monograph.
Response: Comment not incorporated. While the FIEC did review the provided monograph and found similarities to the proposed monograph in *FCC*, they did not support making any changes to the proposed *FCC* monograph based on this information.
Expert Committee Initiated Change #1: The FIEC changed the name from "DHA Algal Oil, *Crypthecodinium* Type" to "DHA from Algal (*Crypthecodinium*) Oil" to remain consistent with more recently adopted naming conventions in *FCC*.

Monograph/Section(s): DHA Algal Oil, *Schizochytrium* Type/Multiple
Expert Committee(s): Food Ingredients
No. of Commenters: 3
Comment Summary #1: The commenter noted inconsistencies in naming the same ingredient in the *FCC* and the *USP-NF* and suggested that the title of the monograph be changed to "DHA Algal Oil (*Schizochytrium*)" to reflect the product being sold and the Latin binomial of the source organism.
Response: Comment not incorporated. The FIEC did not want to establish a title that is inconsistent with other ingredients in the *FCC*.

Comment Summary #2: The commenter requested that the minimum amount of DHA in the *Definition* be stated as "mg/g" instead of "w/w" to match current industry practice.
Response: This comment does not apply as *FCC* does not have a *Definition* section and *FCC* does not specify DHA content in the *Description* section.
Comment Summary #3: The commenter requested that the proposed *Identification* test and requirements be removed and replaced with a requirement that the ingredient "is characterized by significant amounts of long-chain C22 fatty acids. The sum of the area peak for DHA methyl esters is not less than 30%." The commenter stated that the current proposed test and specifications under *Identification* are unnecessarily prescriptive and restrictive and that the limits on the other fatty acids that have been proposed by the FIEC have no relevance to the safety or functional properties of the oil, nor do they characterize the oil. The commenter further stated that the current proposed specifications provide a commercial advantage to the manufacturer whose product was used as the basis for the limits and that this approach is inconsistent with the approaches taken by regulatory agencies in Australia, Brazil, Canada, China, Europe, Indonesia, and Korea and that it is inconsistent with voluntary guidelines used by industry.
Response: Comment not incorporated. The FIEC considers the fatty acid composition profile proposed in the *Identification* section crucial to proper identification of the ingredient and necessary to differentiate oils from different sources. This approach is used in all other monographs for fats and oils in *FCC* and could potentially be used to determine if the ingredient is adulterated.
Comment Summary #4: The commenter requested that the unit of measure for inorganic impurities be listed as "mg/kg" to remain consistent with global regulations and industry policy.
Response: Comment not incorporated. The proposed monograph already gives specifications for *Inorganic Impurities* (*Arsenic, Lead,* and *Mercury*) in mg/kg units.
Comment Summary #5: The commenter requested that the *Labeling* requirement be changed to state the content of DHA as a percentage and not as mg/g. The commenter stated that product certificates of analysis already provide customers with information regarding the DHA content in mg/g and that these certificates, and not the product labels, are used by customers to accept product shipments. Furthermore, the commenter believes that a requirement to add the DHA content in mg/g to product labels does not provide a measurable benefit to the integrity of the product and would result in unnecessary customer notifications.
Response: Comment incorporated, with changes. The FIEC had concerns that all users of the monograph will not calculate percent DHA in the same manner (uncorrected to an internal standard or correction factor), which could cause

inconsistencies in reporting the content of DHA. For this reason the FIEC changed the *Labeling* such that the label provides the content of docosahexaenoic acid (DHA) in “mg/g (%)”.

Comment Summary #6: The commenter requested that the requirement under *Labeling* to list the concentration of added antioxidants on product labels be deleted from the monograph since the products are manufactured according to applicable U.S. and global regulations, which do not require such a quantitative declaration. Furthermore, the commenter noted that the addition of the antioxidant concentration to labels is overly burdensome to manufacturers and does nothing to further ensure the safety or quality of the product.

Response: Comment incorporated.

Comment Summary #7: The commenter requested that the *Function* of the ingredient be changed from “nutrient” to “nutrient ingredient.”

Response: Comment not incorporated. The FIEC did not receive justification for this request and noted that *FCC* does not currently use the function “nutrient ingredient” for any other monographs. Furthermore, since the term “nutrient” is ambiguous, the FIEC deleted that term from the *Function*, leaving “Source of DHA” as the *Function* of the ingredient.

Comment Summary #8: The commenter questioned the need for this monograph and their belief that this ingredient is not widely manufactured. The commenter also questioned whether this monograph is useful to the food industry.

Response: Comment not incorporated. The FIEC believes that the *FCC* should be a source of public standards for commercially-available food ingredients, of which this is one. The FIEC considers a public standard useful to ingredient manufacturers, formulators, food manufacturers, and consumers.

Comment Summary #9: The commenter stated that there is a voluntary industry monograph that was developed in conjunction with manufacturers of DHA products and provided a copy of the specifications required by this monograph. The commenter provided information regarding the group that developed the voluntary monograph and requested that the FIEC review the monograph.

Response: Comment not incorporated. While the FIEC did review the provided monograph and found similarities to the proposed monograph in *FCC*, they did not support making any changes to the proposed *FCC* monograph based on this information.

Expert Committee Initiated Change #1: The FIEC changed the name from “DHA Algal Oil, *Schizochytrium* Type” to “DHA from Algal (*Schizochytrium*) Oil” to remain consistent with more recently adopted naming conventions in *FCC*.

Expert Committee Initiated Change #2: The FIEC noted, in reference to the *Description* section, that the color of this oil could be lighter than what one might consider yellow. To accommodate lighter-colored oils, the FIEC changed the *Description* to replace “yellow to orange” with “light yellow to orange”.

Monograph/Section(s): Isopropyl Alcohol/Assay
Expert Committee(s): Food Ingredients
No. of Commenters: 0
Expert Committee Initiated Change #1: The FIEC changed the wording of *Suitability requirement 1* under *System suitability* from "The relative standard deviation for each peak area is NMT 1.0%" to "The relative standard deviation for the isopropyl alcohol peak is NMT 2.0%." The original requirement was overly restrictive and not necessary. The new requirement meets the needs of the analysis and is based on data submitted.
Expert Committee Initiated Change #2: The FIEC changed the signal-to-noise ratio required in *Suitability requirement 2* under *System suitability* from "NLT 500" to "NLT 10". The original requirement was higher than necessary to establish the suitability of the method. The new requirement was based on data provided by the USP laboratory.

Monograph/Section(s): Maltitol/Loss on Drying
Expert Committee(s): Food Ingredients
No. of Commenters: 1
Comment Summary #1: The commenter requested allowing use of either method (Karl Fisher or Loss on Drying) to determine water content.
Response: Comment not incorporated. Data submitted indicated that results from the two methods are not comparable due to the different principles for measuring water used by the two methods.

Monograph/Section(s): Zeaxanthin/Meso-Zeaxanthin/Multiple
Expert Committee(s): Food Ingredients
No. of Commenters: 1
Comment Summary #1: The commenter requested that the title of the monograph be changed from "Zeaxanthin" to "Meso-Zeaxanthin" to represent the stereoisomer of greatest abundance in the ingredient, the (3*R*,3'*S*-meso) isomer as opposed to the (3*R*,3'*R*) isomer which is traditionally referred to as zeaxanthin. The commenter stated that the title "Zeaxanthin" should be reserved for an ingredient comprised of primarily the (3*R*,3'*R*) isomer.
Response: Comment incorporated.
Comment Summary #2: The commenter requested that the structure included in the proposed monograph be replaced with the structure for the predominant (3*R*,3'*S*-meso) isomer to accurately represent the ingredient described by the monograph.
Response: Comment incorporated.
Comment Summary #3: The commenter requested that the CAS number in the monograph be changed from "144-68-3" to "31272-50-1" which is the correct CAS

number for the predominant (3*R*,3'*S*-meso) isomer. Again, this request is so the CAS number will accurately represent the ingredient described by the monograph.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that "source of zeaxanthin" be deleted from the *Function* section for this ingredient as only a small amount of (3*R*,3'*R*) zeaxanthin (which is the isomer present in the human diet) is present in the ingredient described by the monograph, thus this ingredient is not a significant source of "zeaxanthin".
Response: Comment incorporated with changes. The FIEC acknowledged that the item is not a significant source of (3*R*,3'*R*) zeaxanthin and replaced the words "Source of zeaxanthin" with "Source of meso-zeaxanthin" under *Function*.
Comment Summary #5: The commenter requested that we add a test for the isomeric composition of the product with separate acceptance criteria for each of the two main isomers, (3*R*,3'*R*) and (3*R*,3'*S*-meso) zeaxanthin. The commenter suggested that, since the product is mixed isomers, the exact isomeric composition should be specified.
Response: Comment not incorporated. The commenter did not provide a test method, proposed specifications, or supporting data for this request. This suggestion will be considered in a future *FCC Forum* upon the receipt of a validated method, validation and supporting batch data, and proposed specifications.
Expert Committee Initiated Change #1: The FIEC added the following synonyms for meso-zeaxanthin under the title of the monograph to more accurately describe the chemical composition of the ingredient: *β*,*β*-Carotene-3,3'-diol, (3*R*,3'*S*) and (3*R*,3'*S*-meso)-zeaxanthin.
Expert Committee Initiated Change #2: The FIEC decided that the *Description* section should better describe the ingredient as a racemic mixture of two stereoisomers, (3*R*,3'*R*) and (3*R*,3'*S*-meso) zeaxanthin and, thus, changed the section to read "Meso-Zeaxanthin occurs as a free-flowing, orange to pale yellow powder. It is the purified fraction obtained from isomerization of lutein from *Tagetes erecta* L., which contains both the (3*R*,3'*S*-meso)-zeaxanthin and the (3*R*,3'*R*)-zeaxanthin isomers with approximate concentrations of 94% and 6% (of total zeaxanthin), respectively. It is sparingly soluble in chloroform and practically insoluble in water and ethanol." The approximate concentrations of the isomers are based on data submitted.
Expert Committee Initiated Change #3: The FIEC changed the name of the USP Reference Standard associated with this monograph from "USP Zeaxanthin RS" to "USP Meso-Zeaxanthin RS" to more accurately represent the chemical and to remain consistent with the monograph.