CHEM GUIDANCE

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U. S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
March 2002

Guidance for Industry

Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations

FINAL GUIDANCE

March 2002

Comments and suggestions regarding this document may be submitted at any time. Submit Comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD, 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register (Docket No: 99D-4575).

For questions on the content of the document contact the Office of Food Additive Safety (OFAS), Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), 5100 Paint Branch Parkway, College Park, Maryland 20740-3835, (Tel) 202-418-3087.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition (CFSAN)
March 2002

HIGHLIGHTS OF THE 2001 GUIDANCE

This document contains FDA's recommendations pertaining to chemistry information that should be submitted in a food contact notification (FCN) or food additive petition (FAP) for a food-contact substance (FCS). These recommendations constitute a consolidation and revision of two previous documents: the September, 1999 document "Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations," and the June, 1995 document "Recommendations for Chemistry Data for Indirect Food Additive Petitions." This document also takes into account industry comments on the September, 1999 guidance document for the FCN process. Highlights of the 2001 Guidance document include:

- Alternate approaches to estimating migration to food, such as migration modeling, are presented.
- Consumption factors (CFs) for several specific polymer packaging categories, such as polyethylene terephthalate (PET), polyolefins, polystyrene, cellophane, and nylons, have been

updated.

- Testing for "wet-end" additives used in the manufacture of paper and paperboard is discussed.

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This guidance represents FDA's current thinking on the Chemistry Recommendations for preparation of Food Contact Substances. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the

requirement of applicable statutes and regulations. This guidance is being issued in accordance with FDA's Good Guidance Practices regulation (21 CFR 10.115).

I. INTRODUCTION

Section 309 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended section 409 of the Federal Food, Drug, and Cosmetic Act (the Act) to establish a food contact notification (FCN) process as the primary means by which FDA regulates food additives that are food contact substances (FCSs). An FCS is any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if the use is not intended to have any technical effect in the food (sec. 409(h)(6) of the Act).

An FCS that is a food additive must be regulated for its intended use in 21 CFR Parts 173-178, be exempted from regulation under the agency's Threshold of Regulation Process (21 CFR 170.39), or be the subject of a notification under section 409(h) of the Act that is effective (sec. 409(a)(3) of the Act). Both FCNs and food additive petitions (FAPs) for FCSs must contain sufficient scientific information to demonstrate that the substance that is the subject of the notification or petition is safe under the intended conditions of use (secs. 409(h)(1) and 409(b) of the Act). Because the safety standard is the same for all food additives, whether subject to the petition process or the FCN process, the data and information that should be included in an FCN or FAP are comparable.

Section 409(b) of the Act sets forth the statutory requirements for data in an FAP to establish the safety of a food additive. These requirements include descriptions of the following: (1) the identity of the additive, (2) proposed conditions of use of the additive, (3) technical effect data, and (4) methods for the analysis of the additive. Because substances previously regulated as "indirect food additives" under the FAP process are now authorized through the food contact notification process, this guidance document is intended to replace the guidance document entitled "Recommendations for Chemistry Data for Indirect Food Additive Petitions," dated June 1995.

II. CHEMISTRY INFORMATION FOR FCNS AND FAPS

A clear and concise presentation of the information in the format described below will facilitate review of the FCN or FAP. For notifications, references to the corresponding section(s) in FDA Form 3480, "Notification for New Use of a Food Contact Substance," are shown in italics.

For those uses resulting in dietary concentrations at or below 0.5 ppb, the data requirements for food contact notifications will be similar to those required for requests submitted under 21 CFR 170.39 (Threshold of Regulation) for substances used in food-contact articles. Specifically, the chemistry information requirements will be similar to those cited in 21 CFR 170.39 (c)(1) and (2). As indicated in 21 CFR 170.39(c)(1), the submission will need to include a description of the chemical composition of the food contact substance. This would include identity information on the food-contact substance as well as the identities and composition by weight of all likely impurities (i.e., residual starting materials, catalysts, adjuvants, production aids, by-products and breakdown products). Detailed information may be needed where there are specific safety concerns. Providing additional manufacturing information may be the easiest way to address such concerns. For example, manufacturing information may be used to support the conclusion that a

volatile chemical is unlikely to remain with the finished food-contact substance because of the high temperatures encountered during the manufacturing process. Similarly, information on the types of solvents used in the manufacturing process along with solubility data of likely impurities may be used to justify a conclusion that an impurity is not likely to be found in the finished food-contact substance. As indicated in 21 CFR 170.39(c)(2), the submission will need to include detailed information on the conditions of use of the substance. This would include a statement describing the technical effect of the substance. FDA has not ordinarily needed data to demonstrate the technical effect for uses that meet the threshold of regulation criteria under 21 CFR 170.39.

A. Identity

(see FDA Form 3480- Part II, Sections A through C)

Identity information is used to describe the FCS that is the subject of an FCN or FAP and to identify substances that may migrate into food from use of the FCS. Migrating substances may include not only the FCS itself, but also degradation products and impurities in the FCS.

Information identifying the FCS should be as complete as possible with respect to its name, composition, and method of manufacture. These items include:

1. Chemical Name. The Chemical Abstracts or IUPAC name is acceptable.

2. Common or Trade Names. These should not be the only means of identification. FDA does not maintain a compilation of common or trade names.

3. Chemical Abstracts Service (CAS) Registry Number. [1]

4. Composition. A full description of the composition of the FCS is used to compile a list of potential migrants to food. This should include chemical formulae, structures, and molecular or formula weights for single compounds or components of commercial mixtures. For polymers, notifiers/petitioners should submit the weight average (M_w) and number average (M_n) molecular weight, the molecular weight distribution, and the methods used for their determination. If the molecular weight is not readily obtainable, a notifier/petitioner should furnish other properties of the polymer that are functions of the molecular weight, such as intrinsic or relative viscosity or melt flow index.

   In addition, notifiers/petitioners should provide the following information:

   a. A complete description of the manufacturing process, including purification procedures, and the chemical equations for all steps of the synthesis.

   b. A list of reagents, solvents, catalysts, purification aids, *etc.,* used in the manufacturing process, the amounts or concentrations used, their specifications, and their CAS Reg. Nos.

   c. Chemical equations for known or likely side reactions occurring during

manufacture of the FCS, including catalyst degradation reactions.

d. Concentrations of all major impurities (e.g., residual starting materials, including all reactants, solvents, and catalysts, in addition to byproducts and degradation products) together with supporting analytical data and calculations. In the case of polymers, concentrations of residual monomers should be included.

e. Spectroscopic data to characterize the FCS. In some cases an infrared (IR) spectrum is sufficient, but occasionally other information, such as visible and ultraviolet absorption spectra or nuclear magnetic resonance (NMR) spectra, are more useful.

Those data and information not intended for public disclosure, such as trade secret or confidential commercial information, should be so identified.

5. Physical/Chemical Specifications. Notifiers/petitioners should submit the physical and chemical specifications of the FCS (e.g., melting point, impurity specifications) as well as properties that can affect migration potential, such as solubilities in food simulants. In the case of new polymers, notifiers/petitioners should provide glass transition temperatures, ranges for densities and melt flow indices, and information on morphology (e.g., degree of crystallinity) and stereochemistry. For new adjuvants in regulated polymers, notifiers/petitioners should submit information on the properties of the polymer (e.g., T_g) used in migration testing (see Appendix II. Section 2. for further discussion).

6. Analyses. If the FCS is intended for use as a component of an otherwise regulated material (e.g., an antioxidant in a regulated polymer), notifiers/petitioners should provide analytical methods for determining the concentration of the FCS in the material. Supporting analytical data should be submitted (refer to Section D.3.).

B. Use

(See FDA Form 3480- Part II, Sections D.1 and D.2)

Notifiers/petitioners should examine general use limitations in effective notifications and regulations for similar FCSs and should include a comprehensive set of limitations on the intended use. Certain of these limitations may be the basis for assumptions made in deriving exposure estimates for the FCS. For an FCN, any applicable limitations can be included in the description of the notified use by way of a draft acknowledgement letter. For an FAP, any applicable limitations should be included in draft language for the applicable regulation. In the absence of appropriate limitations, FDA may be required to use assumptions in estimating exposure that would result in more conservative values for certain classes of FCSs.

1. Notifiers/petitioners should provide the maximum use level of the FCS and the types of food-contact articles in which it may be used. "Use level" refers to the concentration of a substance in the food-contact article, not in the food. Notifiers/petitioners should state the range of possible uses, such as films, molded

articles, coatings, etc., and report the anticipated maximum thickness and/or weight per unit area of these articles.

2. Notifiers/petitioners should state whether the intended use for the food contact substance is in single-use or repeat-use food-contact articles. Notifiers/petitioners should also identify the types of food (with examples) expected to be used in contact with the FCS and the maximum temperature and time conditions of food contact[2]. Classifications that may be helpful are given in 21 CFR 176.170(c), Table 1 (Types of Raw and Processed Foods) and Table 2, which lists various conditions of use for single-use applications. These tables are not all-inclusive.

C. Intended Technical Effect

(See FDA Form 3480- Part II, Section D.3)

Notifiers/petitioners should present data to show that the FCS will achieve the intended technical effect and that the proposed use level is the minimum level required to accomplish the intended technical effect. "Technical effect" refers to the effect on the food-contact article, not on the food. An example would be the effect of an antioxidant in preventing oxidative degradation of a particular polymer. In the case of a new polymer, notifiers/petitioners should present data that demonstrate the specific properties of the polymer that make it useful for food-contact applications. This information is frequently available in product technical bulletins.

In cases where the use level of an FCS is self-limiting, notifiers/petitioners should provide supporting data.

D. Migration Testing & Analytical Methods

(See FDA Form 3480- Part II, Section F)

Notifiers/petitioners should provide information sufficient to permit estimation of the daily dietary concentration of the FCS, i.e., consumer exposure. FDA will calculate the concentration of the FCS expected in the daily diet based on analyzed or estimated levels of an FCS in food or food simulants. A more complete discussion of this topic is given in Section II.E. and Appendix IV.

The concentration of an FCS in the daily diet may be determined from measured levels in food or in food simulants, or estimated using information on formulation or residual levels of the FCS in the food-contact article and the assumption of 100% migration of the FCS to food. Although FDA always has accepted reliable analyses of FCS in real foods, in practice, many analytes are difficult to measure in food. As an alternative, notifiers/petitioners may submit migration data obtained with food simulants that can reproduce the nature and amount of migration of the FCS into food. Because an FCS may be used in contact with many foods with different processing conditions and shelf lives, the submitted migration data should reflect the most severe temperature/time conditions to which the food-contact article containing the FCS will be exposed.

Before undertaking migration studies a notifier/petitioner should consider carefully the potential uses of the FCS. If, for example, use at temperatures no higher than room

temperature is anticipated, it makes little sense to conduct migration experiments that simulate high temperature food contact. Such experiments would lead to elevated levels of the FCS in the food simulants that might, in turn, require a more extensive toxicological data package to support the exaggerated exposure estimate. In some cases where the use level of the FCS is low, it may be possible to dispense with migration studies altogether by assuming 100% migration of the FCS to food. The following example illustrates this approach:

> Consider an adjuvant added prior to the sheet-forming operation in the manufacture of paper. If analysis or calculation shows that the final adjuvant concentration in paper cannot exceed 1 mg/kg and the basis weight of the finished paper is 50 pounds/3000 ft^2, or 50 mg/in^2, then the maximum weight of adjuvant per unit area of paper is 1×10^{-6} g adjuvant/g paper x 50 mg/in^2 = 0.000050 mg/in^2[3]. If all the adjuvant migrates into food and 10 grams of food contacts 1 square inch of paper (FDA's default assumption), the maximum concentration in food would be 5 µg/kg. It may be expected that this low concentration in food would lead to a commensurately low dietary concentration for the FCS. Therefore, although migration studies which could result in further lowering of the estimate of daily intake, such studies might be unnecessary.

Levels in food should be based on the results of migration testing or other methods as applicable, so as to reflect as closely as possible the actual use conditions of the food-contact article containing the FCS. In general, migration values determined using the assumption of 100% migration to food should be avoided to reduce conservatisms to the greatest extent possible.

1. Design of the Migration Experiment

   (See FDA Form 3480- Part II, Section F, item 1)

   a. *MIGRATION CELL.* When use of an FCS is anticipated with one particular type of food-contact article, such as a beverage bottle, articles may be filled with food simulants and tested. For more general uses or when the surface area of the food-contact article does not produce sufficient extractives for adequate characterization, a migration cell should be used in which a specimen of known surface area is extracted by a known volume of simulant. The two-sided migration cell described in an article by Snyder and Breder (Snyder and Breder, **1985**) is recommended. Although this specific cell may not be universally applicable, FDA recommends that two of its essential features be incorporated in modified designs. These are:

      (1) Polymer plaques of known surface area and thickness (see Section II.D.1.b. for further discussion) are separated by inert spacers (such as glass beads) so that simulant flows freely around each plaque. Migration from the plaque is considered to be two-sided.

      (2) The headspace is minimized, and gas-tight and liquid-tight seals are maintained. (Minimum headspace and gas tightness are of lesser importance if the migrant of interest is non-volatile.)

Additionally, and importantly, the cell should be subjected to mild agitation to minimize any localized solubility limitation that might result in mass-transfer resistance in the food simulant.

For applications in which a two-sided cell design is not suitable, such as laminate constructions, notifiers/petitioners may refer to the references in Appendix V. for applications describing other cell designs. Notifiers/petitioners also may devise an alternative cell. FDA is willing to comment on any such design prior to performance of the migration experiment.

b. TEST SAMPLE. Some important considerations are the following:

(1) *Formulation:* Notifiers/petitioners should use the highest proposed concentration of the FCS in the food-contact article in preparing samples for migration testing. Notifiers/petitioners should provide information that characterizes resin samples used in testing, including the concentrations and identities of other components that may be present, the chemical composition of the resin (including co-monomer content where appropriate), molecular weight range, density, and melt flow index. If the formulation is plasticized, the most highly plasticized formulation should be used for testing.

(2) *Sample Thickness & Surface Area:* Notifiers/petitioners should report both the thickness of the test plaque and surface area of the sample tested. If a plaque is tested by immersion and is of sufficient thickness to ensure that the initial FCS concentration at its center is unaltered by migration that occurs from both sides during the test period, the surface area of both sides may be used to calculate migration (units of mg/in^2).

Migration may be considered to be independent from both sides of the sample if the sample plaque thickness is at least 0.05 cm (20 mil or 0.020 in) and not more than 25 percent of the FCS has migrated by the end of the experiment. If these conditions are not met, the surface area of only one side should be used in the calculation and consideration should be given to proposing a limitation on film thickness.

(3) *Polymer properties:* If the FCS is a polymer adjuvant, notifiers/petitioners should perform migration testing on the polymer with the lowest average molecular weight which complies with the specifications set in 21 CFR 177 (see Appendix II. Section 2. for further discussion). If the FCS is a new polymer, the polymer that would be expected to give the highest levels of extractives, *i.e.*, the polymer with the lowest average molecular weight, percent crystallinity, and degree of cross-linking should be tested.

c. *FOOD SIMULANTS.* The following food simulants are recommended. Additional discussion on this subject is found in Appendix I.

Food-Type as defined in 21 CFR	Recommended

176.170(c) Table 1	Simulant
Aqueous & Acidic Foods (Food Types I, II, IVB, VIB, and VIIB)	10% Ethanol[a]
Low- and High-alcoholic Foods (Food Types VIA, VIC)	10 or 50% Ethanol[b]
Fatty Foods (Food Types III, IVA, V, VIIA, IX).	Food oil (e.g., corn oil), HB307, or Miglyol 812[c]

[a]for exceptions, see main text.
[b]actual ethanol concentration may be substituted (see main text and Appendix II.).
[c]HB307 is a mixture of synthetic triglycerides, primarily C_{10}, C_{12}, and C_{14}. Miglyol 812 is derived from coconut oil (see main text and Appendix I.).

When food acidity is expected to lead to significantly higher levels of migration than with 10% ethanol, or if the polymer or adjuvant is acid-sensitive, or if trans-esterification occurs in ethanol solutions, separate extractions in water and 3% acetic acid in lieu of 10% ethanol should be conducted. (4)

10% Ethanol is intermediate in alcohol concentration between wine and beer. Migration levels to wine and beer are not expected to be very different from 10% ethanol values. Therefore, test results developed with 10% ethanol may generally be used to evaluate exposures and support clearances for contact with alcoholic beverages with up to 15 volume % ethanol.

Unsaturated food oils (like corn and olive oils) can at times be difficult matrices for the analysis of a migrant because these oils are susceptible to oxidation, especially at high temperature. Miglyol 812, a fractionated coconut oil having a boiling point range of 240° to 270°C and composed of saturated C_8 (50-65%) and C_{10} (30-45%) triglycerides, is an acceptable alternative fatty-food simulant for migration testing.(5) HB 307, a mixture of synthetic triglycerides, primarily C_{10}, C_{12}, and C_{14}, also is useful as a fatty-food simulant.(6)

In some cases, analysis of a migrant in a food oil will not be practical and a simple solvent must be used. There does not appear to be one solvent that will effectively simulate a food oil for all polymers. A list of various polymers and their recommended fatty-food simulants appears in Appendix I. For other polymers, notifiers/petitioners should consult with FDA concerning use of an appropriate fatty-food simulant before performing migration experiments.

The simulant volume should ideally reflect the volume-to-specimen surface area ratio expected to be encountered in actual food packaging. A ratio of 10 mL/in^2 is acceptable. Other ratios may be acceptable if migration levels do not approach concentrations reflecting the partition limit (i.e., the solubility of the FCS in the food simulant). Precipitation of the FCS from solution or a cloudy solution is an indication that this limit has been reached. The volume-to-surface area ratio should be reported.

d. *TEMPERATURE AND TIME OF TEST.* Notifiers/petitioners should conduct migration testing under the most severe conditions of temperature and time anticipated for the proposed use. If the intended use of the FCS involves contact with food at temperatures higher than room temperature, tests should be conducted at the highest use temperature for the maximum expected time period. In many instances, short time periods of elevated temperature-food contact are immediately followed by extended periods of storage at ambient temperatures. For such applications, FDA's recommended migration protocols call for short-term accelerated testing designed to simulate FCS migration that may occur during the entire food-contact period. Recommended protocols for selected situations are given in Appendix II.; however, depending on the particular food-contact application, a specific protocol may be devised.

For room-temperature applications, a test temperature of 40°C (104°F) for 10 days is recommended. This accelerated testing protocol is based on studies showing that experimental migration levels were roughly equivalent to levels obtained after extended storage (6-12 months) at 20°C (68°F) [7].

For refrigerated or frozen food applications, the recommended test temperature is 20°C (68°F).

For polymers, such as polyolefins, that are used with food at temperatures above their glass transition temperatures (i.e., the polymer is in the rubbery state), the highest migration values (typically, but not always, the ten day values) are generally used by FDA to calculate the concentration of migrants in food.

Polymers such as polyethylene terephthalate (PET) and polystyrene (PS), however, are used with food at temperatures below their glass transition temperatures (i.e., the polymer is in the glassy state). At a fixed temperature, the rate of diffusion of migrants through a polymer in the glassy state is lower than if the polymer were in the rubbery state. For this reason, accelerated testing for 10 days at 40°C might underestimate migration that would occur during the entire food-contact scenario. Therefore, migration data obtained over ten days at 40°C should be extrapolated to 30 days in order to better approximate migration levels expected after extended time periods at ambient conditions. The notifier/petitioner may carry out testing for 30 days to avoid uncertainties in extrapolation. If data are provided that demonstrate that a different extrapolation period is more appropriate for a given adjuvant/polymer combination, such information would be used for evaluating exposure.

For restricted uses where the maximum shelf life and food-contact temperature

of an article are known, notifiers/petitioners are encouraged to carry out migration studies for the maximum shelf life under temperature conditions approximating expected use. Notifiers/petitioners may want to consult FDA before undertaking such tests.

For each migration experiment, FDA recommends that portions of the test solutions should be analyzed during at least four time intervals. Recommended sampling times for a ten-day test are 2, 24, 96, and 240 hours. FDA recommends analysis of a blank or control using a test cell identical to that used for the test article.

e. *END TESTS (Compliance Tests).* It is important to realize that the appropriate migration test conditions for a new FCS are not those described in 21 CFR 175.300, 21 CFR 176.170 or other sections in 21 CFR. These published "end-test" extractions are quality control test methods that are used to verify whether a particular product is equivalent to the material that served as a basis for the approval. End tests bear no relation to the migration testing recommended for evaluating probable exposure to a new FCS.

2. Characterization of Test Solutions & Data Reporting

(See FDA Form 3480- Part II, Section F, item 1)

Notifiers/petitioners should perform migration studies in triplicate and analyze the test solutions for the migrants.

If the FCN or FAP is for a polymer, notifiers/petitioners should determine the amount and nature of total nonvolatile extractives (TNEs). Ordinarily, the TNEs are determined gravimetrically. The nature of the extractives, which may include monomers, oligomers, adjuvants, and catalyst residues, should be determined by suitable chemical or physical tests, such as NMR, UV-visible, and atomic absorption spectroscopy, mass spectrometry, and gas or liquid chromatography. The limit of quantitation and selectivity of the methods used should be indicated in the FCN or FAP. If quantitation of individual migrants is not possible, notifiers/petitioners should determine the distribution of the extractives between organic and inorganic fractions by solvent fractionation (i.e., the fraction of the TNE residue that is soluble in chloroform). This serves, as a first step, to focus on the migrants of interest (e.g., organic components) in determining exposure estimates. In these instances, FDA generally will estimate exposure to TNEs from the use of the FCS assuming that the TNEs (or chloroform-soluble TNEs) consist solely of low molecular weight oligomers that are chemically equivalent. Because the degree of toxicological testing depends on the magnitude of the exposure estimate, it should be to the notifier's/petitioner's advantage to quantitate the components in the TNEs that are not chemically equivalent (e.g., differentiate between low molecular weight oligomers and polymer adjuvants).

Test solutions from polymers that are the subject of an FCN or FAP also should be analyzed for constituent monomers. Alternatively, the known residual monomer level in the polymer may be used to calculate monomer dietary concentrations by using the density of the polymer, the maximum anticipated thickness of the food-contact

article, and by assuming that all of the residual monomer migrates into food and that ten grams of food contact one square inch of food-contact article.

If the FCN or FAP is for a polymer adjuvant, the test solutions are generally analyzed only for the adjuvant. Occasionally, however, it may be appropriate to quantitate, in the test solutions, impurities or decomposition products present in the adjuvant if they might be expected to become components of the daily diet in toxicologically significant quantities. A common example would be the presence of carcinogenic impurities in the adjuvant.

It also may be appropriate to quantitate, in the test solutions, decomposition products produced either as a result of the FCS exhibiting its intended technical effect in the food contact article or in the test solutions after migration of the FCS. An example would be the use of a new antioxidant for polyolefins. Polymer antioxidants, by their very nature, would be expected to partially decompose during thermal processing of the resin or food-contact article containing the substance. Frequently, decomposition also occurs after migration of the FCS into food or food simulant, where temperatures may reach 120°C with fatty-food simulants. Information on decomposition in the food simulants may be obtained by conducting stability studies on the FCS in parallel with the migration studies.

Notifiers/petitioners should report results in terms of milligrams of substance extracted per square inch (mg/in^2) of surface area. Migration amounts often are expressed in terms of mg/dm^2. The mixed unit mg/in^2 is preferred, however, to facilitate conversion to concentration in food. If ten grams of food are in contact with one square inch of food-contact article surface, a migration of 0.01 mg/in^2corresponds to a concentration in food of 1 mg/kg. For specialized food-contact applications where an assumed ratio of 10 g food per in^2 is not appropriate, such as in dual-ovenable trays and microwave heat-susceptor applications, notifiers/petitioners should use the lowest ratio from the actual food-contact applications and should provide justification for the ratio selected.

3. Analytical Methods

(See FDA Form 3480- Part II, Section F, item 1)

Notifiers/petitioners should submit the following for each method:

a. *DESCRIPTION OF THE METHOD.* The description should include discussions on the procedure's accuracy, precision, selectivity, limit of quantitation (LOQ), and limit of detection (LOD). [8] Sufficient detail should be provided so that it can be followed by an experienced analytical chemist. If a literature reference is available, a copy should be included in the FCN or FAP.

b. *STANDARD CURVES.* Standard curves or calibration curves obtained by analyzing a prepared medium fortified with several known amounts of analyte to obtain concentrations both greater than, and less than, the concentration of migrant in the test solutions. The prepared medium may be the pure solvent, a solution of known ionic strength, etc. The data points from which the standard

curve is derived should bracket the concentration of the migrant in the test solution. An analyte concentration of 1 mg/kg determined from a standard curve obtained from concentrations of 10, 15 and 20 mg/kg would be unacceptable. The correlation coefficient and standard errors of the Y intercept and the slope should be reported with the standard curve.

c. *EXAMPLES OF SPECTRA OR CHROMATOGRAMS.* Notifiers/petitioners should limit sample spectra and chromatograms, clearly identifying and labeling all major peaks to avoid ambiguities in interpretation.

d. *EXAMPLE CALCULATIONS.* Notifiers/petitioners should limit example calculations relating the data obtained from instrumental methods to the reported levels (preferably in milligrams migrants per square inch of sample surface area). The examples allow the reviewer to perform a rapid internal check on the reported method.

e. *VALIDATION OF ANAYLTICAL METHODS.* Notifiers/petitioners should properly validate all analytical methods. Validation of a method's intended use, the determination of accuracy and precision, usually involves: 1) replicate analyses of appropriate matrices fortified with known amounts of the analyte, at concentrations similar to those encountered in the migration studies, and 2) determination of the percentage recovery of the fortified analyte. In cases where a polymer adjuvant is the subject of interest, test solutions of the polymer formulated without the adjuvant may serve as the matrix for fortification and recovery measurements. Recovery is defined as the difference between measured analyte levels in the fortified and unfortified matrices. Percent recovery is the recovery divided by the fortified level times 100, i.e., if "a" is the measured level in the unfortified solution, "b" is the measured level in the fortified solution and "c" is the fortification level, then percent recovery equals (b-a)/c x 100.

If migration test solutions are fortified, they should be fortified before analytical workup but after the prescribed test time, *e.g.,* 240 hours. The actual test solutions must be fortified and not the pure food simulants. Fortification of pure simulants instead of the test simulants is probably the most common deficiency in the validation section of an analytical method.

Notifiers/petitioners should perform fortification and recovery experiments using three (3) sets of triplicate samples of the test simulants with each set fortified at a separate level. The fortification levels should be one-half (½), one (1), and two (2) times the measured concentration of the analyte in the food simulant. In the event that the FCS is not detected, notifiers/petitioners should determine the LOD for the method. For quantifiable levels of the analyte, acceptable recoveries should meet the following criteria:

Levels in food or food simulants[(a)]	**Acceptable average recovery**	**Acceptable relative standard deviation**

<0.1 mg/kg	60-110%	<20%
>0.1 mg/kg	80-110%	<10%
[a]If 0.001 mg of a substance is extracted from one square inch of packaging material into 10 grams of food or food simulant, the estimated concentration in food is 0.1 mg/kg.		

In evaluating the precision of the analytical method, the variability arising from analyses of individual samples can be eliminated by performing triplicate analyses on a homogeneous composite (a blend of the triplicate samples) where practicable.

Other validation procedures may be appropriate depending on the particular analysis. For example, analysis of the same test solution by two independent analytical methods would be acceptable validation. Similarly, the method of standard additions is an acceptable alternative in certain cases, such as metal analysis by atomic absorption spectroscopy. In this case, fortify the matrix at two separate concentrations (at least) in addition to the unfortified concentration, and verify the linearity of the standard addition curve by calculation of the least squares correlation coefficient (r should be >0.995).

Notifiers/petitioners should submit representative spectra or chromatograms from validation analyses of fortified and blank samples. Spectra or chromatograms of the "blank" will facilitate the verification of the absence of interferences. An illustrative example appears in Appendix III.

4. Migration Database

(See FDA Form 3480- Part II, Section F, item 2)

Migration data for specific migrant/polymer/food simulant systems at given temperatures that exhibit a predictable migration-time behavior, e.g., Fickian diffusion, may be used to predict migration at other temperatures. Thus, the need for migration studies for new applications, which in certain cases such as high temperature applications may be difficult to perform, may be reduced.

For example, migration data obtained over 10 days (240 h) at 40°C that exhibits Fickian behavior, in combination with migration data obtained at other temperatures (e.g., 60°C and 80°C), may be extrapolated by means of an Arrhenius plot to predict migration under retort conditions (121°C/2 h and 40°C/238 h), if no apparent change in polymer morphology, such as glass transition or polymer melting, is expected between 30°C and 130°C. Apparent diffusion coefficients, D, at 121°C for each migrant/polymer/food simulant can be obtained from a plot of ln D vs 1/T(K). Thus, migration for 2 hours at 121°C can be estimated and added to migration after 238 hours at 40°C to obtain total migration expected for retort and ambient storage conditions. The density and thickness of the polymer sample and initial concentration of the migrant in the polymer are also necessary for the calculations.

The FDA migration database is intended as a resource for migration data, including

diffusion coefficients and relevant polymer/additive properties. FDA continues to compile migration data from various sources for use in estimating migration levels for FCSs. Reliable migration data, *e.g.*, data that follow Fickian diffusion, submitted in support of an FCN would be added to the database. In addition, only migration levels that have been measured at three or more time intervals for a given temperature will be considered for inclusion in the migration database. Notifiers/petitioners may submit suitable data for inclusion into the database in the form of a letter, as part of a notification or petition, or in a Food Additive Master File. The FDA migration database is available through the Freedom of Information Act (FOIA) (Also see the CFSAN website at http://www.cfsan.fda.gov/~dms/foia.html).

5. Migration Modeling

(See FDA Form 3480- Part II, Section F, item 2)

As discussed above, migration levels in food are typically estimated based on the results of migration testing under the anticipated conditions of use or, in certain cases, under the assumption of 100% migration of the FCS to food. These two approaches are adequate in most instances.

A third alternative involves migration modeling. One simple approach to modeling migration for *specific* migrant/polymer/food simulant systems, based on select experimental data, was discussed above in Section II.D.4. If this approach is taken, the source of any material constants used in migration modeling should be appropriately referenced, whether the source is the FDA migration database or the open literature.

Recently, semi-empirical methods have been developed to determine migration levels with limited or, in certain cases, no migration data (see, e.g., (Limm and Hollifield, **1996**) and (Baner, et al., **1996**)). These diffusion models rely on estimation of diffusion coefficients based on the nature of the migrant and the physical properties of the polymer. They may be useful substitutes for, or additions to, experimental data under limited circumstances. Several caveats should be considered in the application of such diffusion models. First, distribution of the migrant in the polymer is considered isotropic. Non-isotropic distribution, whether intentional or unintentional, would be expected to result in non-Fickian migration. Two, other aspects of migration, such as partitioning, mass transfer, polymer morphology, shape/polarity of the migrant, and plastization of the polymer are not considered in these models. These factors should be considered carefully when deriving migration levels to food using modeling techniques.

E. CONSUMER EXPOSURE

(See FDA Form 3480- Part II, Section G)

Migration data developed using the procedures outlined in Section II.D. are intended to provide estimates of the highest level of migration to food that might result from the anticipated use of the FCS. FDA estimates probable exposure to the FCS by combining the migration data with information on uses of food-contact articles that may contain the FCS (i.e., on the fraction of a person's diet likely to contact food-contact articles containing the

FCS).

From a given concentration of the FCS in the daily diet, the estimated daily intake (EDI) is calculated as the product of that concentration and the total food intake, assumed to be 3 kilograms per person per day (kg/p/d, solids and liquids). A concentration in the daily diet of 1 ppm corresponds to an EDI of 1 mg FCS/kg food x 3 kg food/p/d, or 3 mg FCS/p/d.

Both the concentration in the daily diet and the EDI from the subject FCN or FAP and the cumulative EDI (CEDI) from all regulated uses and effective FCNs are used by FDA in the safety evaluation of an FCS. The CEDI of the FCS is used to determine the types of toxicity studies necessary to establish safety under the proposed conditions of use. Toxicological data recommendations for several tiers of CEDIs resulting from all proposed and permitted uses of the FCS, including regulated uses, uses that were the subject of previous FCNs, and the use in the subject FCN, are described in the document entitled "Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations."

The approach outlined below is designed to deal with the majority of FCSs intended for single-use. For estimating dietary exposures to components of repeat-use items and articles used in or with food processing equipment, exposure estimates also will consider the amount of food to be contacted during the service life of the food-contact article (see Appendix II. Section 4.).

1. Calculation of Exposure

    a. *CONSUMPTION FACTOR.* The term "Consumption Factor" (CF) describes the fraction of the daily diet expected to contact specific packaging materials. The CF represents the ratio of the weight of all food contacting a specific packaging material to the weight of all food packaged. CF values for both packaging categories (e.g., metal, glass, polymer and paper) and specific food-contact polymers are summarized in Table I of Appendix IV. These values were derived using information on the types of food consumed, the types of food contacting each packaging surface, the number of food packaging units in each food packaging category, the distribution of container sizes, and the ratio of the weight of food packaged to the weight of the package. These values, however, may be modified as new information is received. Several of the values contained in Table I and Table II of Appendix IV have been updated recently.

    When FDA computes exposure to an FCS, it assumes that the FCS will capture the entire market for which it is intended for use. This approach reflects both uncertainties about likely market penetration as well as limitations in the data surveyed. Thus, if a company proposes the use of an antioxidant in polystyrene, it is assumed that the antioxidant will be used in all polystyrene manufactured for food contact. In certain cases where an adjuvant is intended for use in only a part of a packaging or resin category, a lower CF representing the coverage that is sought may be used. For example, if a stabilizer is intended for use only in rigid and semirigid poly(vinyl chloride) (PVC), a CF of 0.05 rather than 0.1 could be used in estimating exposure since only about 50% of all food-contact PVC could contain the stabilizer. Another example is the division of polystyrene into impact and non-impact categories (see Table I, Appendix IV.). To reduce conservatisms, notifiers/petitioners are encouraged to submit as

detailed information as possible on the anticipated resin or packaging market(s) that may be captured by articles manufactured from the FCS.

When new products are introduced, they will initially be treated as replacement items for existing technology. As noted, FDA generally makes estimates based on the assumption that the new product will capture the entire market. For example, the retortable pouch initially was treated as a replacement for coated metal cans and was assigned a CF of 0.17. As additional information on actual use of the retortable pouch became available, the CF was lowered to 0.05. In certain cases, the submission of resin or packaging market data may lead to the use of a lower CF.

b. *FOOD-TYPE DISTRIBUTION FACTOR.* Before migration levels can be combined with CF values to derive estimates of probable consumption, the nature of the food that will likely contact the food-contact article containing the FCS must be known. Migration into a fatty-food simulant, for example, will be of little use in estimating probable exposure if the FCS is used exclusively in or for articles in contact with aqueous food. To account for the variable nature of food contacting each food-contact article, FDA has calculated "food-type distribution factors" (f_T) for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic and fatty. Appropriate f_T values for both packaging categories and polymer types appear in Table II of Appendix IV.

c. *CONCENTRATION IN THE DAILY DIET AND EDI.* FDA uses the following approach for calculating the concentration of the FCS in the daily diet. The concentration of the FCS in food contacting the food-contact article, <M>, is derived by multiplying the appropriate f_T values by the migration values, M_i, for simulants representing the four food types. This, in effect, scales the migration value from each simulant according to the actual fraction of food of each type that will contact the food-contact article.

$$\langle M \rangle = f_{\text{aqueous and acidic}}(M_{\text{10\% Ethanol}}) + f_{\text{alcohol}}(M_{\text{50\% Ethanol}}) + f_{\text{fatty}}(M_{\text{fatty}})$$

where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant.

The concentration of the FCS in the diet is obtained by multiplying <M> by CF. The EDI is then determined by multiplying the dietary concentration by the total weight of food consumed by an individual per day. FDA assumes that an individual consumes 3kg of food (solid and liquid) per day (seeAppendix IV. for sample calculations):

$$\text{EDI} = 3 \text{ kg food/person/day} \times \langle M \rangle \times \text{CF}$$

d. *CUMULATIVE EXPOSURE (CEDI).* If the FCS already is regulated for other uses in 21 CFR 170-199, has been exempted from the need for a regulation under the Threshold of Regulation (21 CFR 170.39), or has been the subject of previous effective FCNs, the notifier/petitioner should estimate the

cumulative exposure to the FCS from the proposed and permitted uses (see the example in Appendix IV.). Information on the regulatory status of an FCS may be obtained by inspection of 21 CFR 170-199, searching the CFR on the Government Printing Office (GPO) World Wide Website at http://www.access.gpo.gov/nara/cfr/index.html, or contacting FDA directly. Information on effective FCNs or Threshold of Regulation exemptions for an FCS may be obtained through the FDA website or by contacting FDA directly. An estimate of cumulative exposure for the regulated, notified and exempted uses of an FCS can be obtained by contacting FDA. FDA also maintains a database of CEDIs for FCSs on the Agency's internet site (http://www.cfsan.fda.gov).

2. Exposure Refinement

Exposure estimates, in general, will be made using the aforementioned procedures. More refined exposure estimates may be possible, however, with additional information provided in an FCN or FAP. For instance, subdividing packaging or resin categories could reduce the calculated exposure by lowering the CF for the category. The division of PVC into rigid and plasticized categories and PS into impact and non-impact categories, cited above, are two examples. Another example is the division of polymer coatings for paper into subcategories, such as poly(vinyl acetate) coatings, styrene-butadiene coatings, etc. If an FCS is to be used solely in styrene-butadiene coatings for paper, use of the CF for polymer-coated paper (0.2, Appendix IV. Table 1) would be a gross exaggeration. As noted above, FDA encourages the submission of information that may be used to subdivide the market(s) anticipated for articles manufactured from the FCS.

In those cases where the nature of the coverage requested may necessitate more detailed information or where a notifier/petitioner believes that exposure will be overstated by simply selecting CF and f_T values presented in Appendix IV., data of the following type may be submitted to facilitate calculations of CF and f_T values for materials likely to contain the FCS:

a. Estimates of the total amount of food in contact with the packaging material determined using either:

   (1) package unit data (number of units and their size distribution), or

   (2) total weight of packaging material produced for food contact, container size distribution, and ratios of weight of food packaged to weight of package.

b. Characterization of the foods that might contact the food-contact article, along with supporting documentation, and the likely f_T values.

c. Information that would demonstrate that only a fraction of a packaging or resin category would be affected by the coverage sought.

d. Technological limitations that could affect the type of food contacted or the

fraction of the diet that might be contacted.

APPENDIX I.

FATTY-FOOD SIMULANTS FOR SPECIFIC POLYMERS

A food oil is the most extreme example of a fatty food. If contact with fatty foods is anticipated, FDA recommends conducting migration studies using a food oil as the food simulant. In addition to food oils, such as corn and olive oil for which extensive migration data already exist, the use of HB307 (a mixture of synthetic triglycerides, primarily C_{10},C_{12}, and C_{14}) as a fatty-food simulant has been recommended. Studies in FDA laboratories have shown that Miglyol 812, a fractionated coconut oil having a boiling range of 240-270°C and composed of saturated C_8 (50-65%) and C_{10} (30-45%) triglycerides, is also an acceptable alternative. Since use of these oils for FCS migration may not always be practicable, the use of aqueous-based solvents that simulate the action of these liquid fats is sometimes necessary. While it seems unlikely that one solvent will be found that simulates the action of a food oil for all food-contact polymers, the following list presents polymers for which adequate data exist to support the use of aqueous-based solvents as fatty-food simulants. The recommendation of these solvents is based upon studies done at FDA, at the National Institute of Standards and Technology (formerly The National Bureau of Standards), and by Arthur D. Little, Inc. under contract to FDA (a list of general references pertaining to these studies is shown in Appendix V). For polymers other than those listed below, notifiers/petitioners should consult FDA before undertaking any migration experiments.

1. Polyolefins complying with 21 CFR 177.1520 and ethylene - vinyl acetate copolymers complying with 21 CFR 177.1350	95% or absolute ethanol
2. Rigid poly(vinyl chloride)	50% ethanol
3. Polystyrene and rubber-modified polystyrene	50% ethanol
4. Poly(ethylene terephthalate)	50% ethanol

Absolute or 95% ethanol has been found to be an effective fatty-food simulant for polyolefins; however, it appears to exaggerate migration for other food-contact polymers.

Previous test protocols (prior to 1988) recommended the use of heptane as a fatty-food simulant. To account for the aggressive nature of heptane relative to a food oil, division of migration values by a factor of five was permitted. Studies have shown, however, that the exaggerative effect of heptane relative to a food oil varies over orders of magnitude depending on the polymer extracted. *Thus, heptane is no longer recommended as a fatty-food simulant.* However, we recognize that in cases where very low migration is anticipated, such as for inorganic adjuvants or certain highly cross-linked polymers, heptane can be useful due to the ease of analytical workup. Because of the known variance in the exaggerative effect of heptane relative to food oil, if heptane is used, migration values will generally not be divided by any factor unless there is adequate justification.

APPENDIX II.

SELECTED MIGRATION TESTING PROTOCOLS

The following migration testing protocols are intended to simulate most anticipated end-use conditions of food-contact articles. These protocols are based on the premise that migration to aqueous- and fatty-based foods is typically diffusion-controlled within the polymer, strongly affected by the temperatures encountered during food contact, and further modified by the solubility of the FCS in the foods. Therefore, migration testing with food simulants at the highest temperatures to be experienced by the food-contact article during food contact is recommended. Testing with actual fatty foods is also an option, although determination of the analytes of interest is often very difficult. In those instances where the expected use conditions are not adequately simulated by these protocols or testing with food simulants at the highest anticipated food-contact temperature is not practical, alternatives to those protocols presented below should be developed in consultation with FDA.

1. General Protocols (Single-Use Applications) Corresponding to Condition of Use

   As noted in Appendix I., migration to fatty foods is evaluated using a fatty food, a pure liquid fat, or, alternatively, aqueous ethanol solutions when analytical limitations preclude sensitive analyses. As noted in Section II.D.1.c., migration to aqueous, acidic, and low-alcoholic foods is generally evaluated using 10% ethanol and migration to high-alcohol foods is generally evaluated using 50% ethanol.

   The recommended migration protocols given below are intended to model thermal treatment and extended storage conditions for polymers, such as polyolefins, used with food at temperatures above their glass transition temperatures. The extended storage period generally involves testing at 40°C for 240 hours (10 days). As discussed in Section II.D.1.d., migration data obtained at 10 days for polymers used below their glass transitions temperature should be extrapolated to 30 days to better approximate migration levels expected after extended storage at ambient conditions.

   A. *High temperature, heat sterilized or retorted above 100° C (212°F)*

10% Ethanol[(a)]	121°C (250°F) for two hours
50% Ethanol	71°C (160°F) for two hours
Food Oil (*e.g.*, corn oil) or HB307 or Miglyol 812	121°C (250°F) for two hours
50% or 95% Ethanol[(a),(b)]	121°C (250°F) for two hours
[(a)]Requires a pressure cell or autoclave, see Appendix V. Appropriate safety precautions should be exercised when using equipment generating pressures above 1 atmosphere. [(b)]Depends on food-contact layer, see Appendix I.	

   After two hours at elevated temperatures, the tests should be continued at 40°C (104°F) for 238 hours to a total of 240 hours (10 days). The test solutions should be analyzed at the end of the initial two hour period, and after 24, 96 and 240 hours.

B. *Boiling water sterilized.* Notifiers/petitioners should use the same protocol as for Condition of Use A except that the highest test temperature is 100°C (212°F).

C. *Hot filled or pasteurized above 66°C (150°F).* Solvents should be added to the test samples at 100°C (212°F), held for 30 minutes, and then allowed to cool to 40°C (104°F). The test cells should be maintained at 40°C (104°F) for ten days with samples taken for analysis after the intervals indicated for the previous protocols. If the maximum hot fill temperature will be lower than 100°C (212°F), test solvents may be added at this lower temperature. Alternatively, notifiers/petitioners should perform migration studies for 2 hours at 66°C (150°F) followed by 238 hours at 40°C (104°F). For the alternative method, the longer time at the lower temperature (2 hours at 66°C vs 30 minutes at 100°C) compensates for the shorter time at 100°C.

Note: migration studies conducted according to condition of use C are only adequate to support conditions of use C through G (not condition of use H).

D. *Hot filled or pasteurized below 66°C (150°F).* The recommended protocol is analogous to that for C except that all test solvents are added to the test samples at 66°C (150°F) and held for 30 minutes before cooling to 40°C (104°F).

E. *Room temperature filled and stored (no thermal treatment in the container).* The notifier/petitioner should conduct migration studies for 240 hours at 40°C (104°F). The test solutions should be analyzed after 24, 48, 120 and 240 hours.

F. *Refrigerated storage (no thermal treatment in the container).* The recommended protocol is identical to that for E except that the test temperature is 20°C (68°F).

G. *Frozen storage (no thermal treatment in the container).* The recommended protocol is identical to F except that the test time is five (5) days.

H. Frozen or refrigerated storage; ready-prepared foods intended to be reheated in container at time of use:

10% Ethanol[(a)]	100°C (212°F) for two hours
Food Oil (*e.g.*, corn oil) or HB307 or Miglyol 812™	100°C (212°F) for two hours
50% or 95% Ethanol[(a),(b)]	100°C (212°F) for two hours
[(a)]Requires a pressure cell or autoclave, see Appendix V. [(b)]Depends on food-contact layer, see Appendix I.	

Applications involving the heating and cooking of food at temperatures exceeding 121°C (250°F) are not included under conditions of use A-H. Migration testing protocols for these applications are discussed in Section 11. of this Appendix.

2. Adjuvants for Polyolefins

In general, under identical testing conditions, levels of migrants from low-density polyethylene (LDPE) are higher than from high-density polyethylene (HDPE) or polypropylene (PP). Migration studies done solely on LDPE (complying with 21 CFR 177.1520(a)(2)) at 100°C (approximately the highest temperature at which LDPE remains functional) are, therefore, generally sufficient to provide coverage for all polyolefins including PP, which may be used for retort applications. In such a case, the CF for all polyolefins (CF = 0.35) generally will be used instead of the individual CF for LDPE (0.12, see Appendix IV. Table I).

Nevertheless, when seeking coverage for use with all polyolefins, it is usually advantageous to perform migration testing on HDPE, PP and linear LDPE (LLDPE), complying with 21 CFR 177.1520, as well as LDPE. By doing this, actual migration values for these polyolefins, which will likely be lower than those obtained from LDPE, may be used to calculate the EDI.

The specific polymer test sample used in the migration testing should be one that has a morphology typically used in food packaging applications. The test material must comply with specifications set out in 21 CFR 177.1520. In addition to noting which specifications listed in 21 CFR 177.1520 apply, information characterizing the polymer resin, such as molecular weight distribution, melt flow index, and degree of crystallinity should be provided.

The catalyst technology for the manufacture of polyolefins is continually being improved. The choice of a particular catalyst technology for the synthesis of polyolefins such as LLDPE, HDPE, and PP determines their unique physical properties, such as molecular weight and melt flow index. These factors should be taken into account when selecting the appropriate test polymer for the adjuvant. In addition, an increase in the comonomer content of a copolymer generally results in a lower melt range, lower density, and lower crystallinity in comparision to the homopolymers. Therefore, for the broadest possible coverage of an adjuvant, migration testing should be conducted on LLDPE, HDPE or PP copolymers (not homopolymers) incorporating the highest comonomer level.

3. Adjuvants for Polymers (other than Polyolefins)
Adjuvants for More than One Polymer

The recommended migration testing protocols for polymers other than polyolefins are the same as those in Section 1. of this Appendix. Appendix I. should be consulted for the recommended fatty-food simulant.

If use of an FCS is sought without limitation to specific polymers, notifiers/petitioners should test with an unoriented LDPE sample complying with 21 CFR 177.1520(a)(2). The test protocol depends on the anticipated conditions of use (refer to Section 1. of this Appendix). If the most rigorous applications correspond to Condition of Use A (Section 1.A.), the test temperature should be the highest temperature at which the polymer remains functional (ca.100°C for LDPE). The CF for all polymers (Appendix IV. Table 1, CF = 0.8) should be used with the migration data to calculate the concentration of the FCS in the daily diet. In general, a lower calculated concentration in the daily diet will result if a series of representative polymers are separately tested and individual consumption factors are applied (refer to the examples in Appendix IV.). Notifiers/petitioners should consult with FDA to determine which representative polymers should be tested.

4. Articles Intended for Repeated Use

The article should be tested with 10% and 50% ethanol and a food oil (e.g., corn oil) or other fatty-food simulant (e.g., HB307 or Miglyol 812) for 240 hours at the highest intended temperature of use. The test solutions should be analyzed for migration of the FCS after 8, 72, and 240 hours. Notifiers/petitioners should provide estimates of the weight of food contacting a known area of repeat-use article in a given time period as well as an estimate of the average lifetime of the article. Together with the migration data, this will allow calculation of migration to all the food processed over the service life of the article.

In the case of an adjuvant in a repeat-use article, FDA strongly recommends an initial calculation of a "worst case" level in food by assuming 100% migration of the adjuvant over the service life of the article and dividing that value by the quantity of food processed. If this calculated concentration is sufficiently low, migration studies will be unnecessary.

5. Coatings for Cans

The migration testing protocol is usually that outlined in Section 1.A. of this Appendix for high temperature, heat sterilized or retorted products. If broad coverage is sought for all types of coatings, notifiers/petitioners should consult with FDA to determine which coatings should be tested. For use conditions less severe than retort sterilization at 121°C, follow the migration test protocols outlined in Sections 1.B.-G. of this Appendix which most closely approximate the most severe expected use conditions.

6. Uncoated & Clay-Coated Papers with Latex Binders

These papers are intended for contact with food at temperatures less than 40°C for short periods of time. The recommended protocol is the following:

10% Ethanol	40°C (104°F) for 24 hours
50% Ethanol	40°C (104°F) for 24 hours
Food Oil (*e.g.*, corn oil) or HB307 or Miglyol 812	40°C (104°F) for 24 hours

Migration studies conducted on uncoated or clay-coated papers typically result in a high level of extractives due to the large number of low-molecular weight, soluble components in both paper and paper coatings. Therefore, when total nonvolatile or chloroform-soluble total nonvolatile extractives are determined for a paper coating, do not subtract the corresponding extractives from uncoated paper as a blank correction. Rather than using paper as a support for the coating, it is often useful to apply the coating to a suitable inert substrate, such as glass or metal, for use in migration testing. For a new adjuvant in paper coatings, the test solutions should be analyzed for the unregulated adjuvant. For a new polymer used in paper coatings, the test solutions should be analyzed for constituent oligomers and monomers.

7. Specially Treated Papers

This class includes such types as fluoropolymer- and silicone-treated papers that have oil-resisting and heat-resisting properties. The specific protocol depends on the particular uses anticipated. It is recommended that the notifier/petitioner either devise a protocol and submit it to FDA for comment or request comment from FDA about appropriate test conditions.

8. Adhesives (Room temperature or below)

In previous chemistry guidance documents for indirect additives, migration tests were not recommended for adhesives intended for use at room temperature or below and in accordance with 21 CFR 175.105. (High temperature applications are discussed in Section 9.). This recommendation was based on consideration of 21 CFR 175.105 (a)(2) which specifies that the adhesive is either separated from food by a functional barrier, or the quantity of adhesive that contacts aqueous and fatty food is limited to the trace amount at seams and edges.

If a notifier/petitioner proposes to use an adhesive or adhesive component in accordance with the limitations of 21 CFR 175.105, migration levels for the substances generally will be assumed to be no greater than 50 ppb. Applying a CF of 0.14 for adhesives gives a dietary concentration of 7 ppb. If the assumptions of 21 CFR 175.105 cannot be supported, data or calculations should be submitted to model the intended use of any adhesive component. If a notifier/petitioner wishes to perform migration testing, multilaminate samples should be fabricated with the maximum anticipated amount of the adhesive component and with the minimum thickness of the food-contact layer. The migration protocol corresponds to condition of use E. Alternatively, migration levels in food can be estimated based on migration modeling (see Section II.D.5.).

9. Laminates & Coextrusions

Components of multilayer structures used above room temperature are the subject of two regulations. One covers laminates used in the temperature range 120°F (49°C)-250°F (121°C) (21 CFR 177.1395) and the other covers laminate structures used at temperatures of 250°F (121°C) and above (21 CFR 177.1390). Layers not separated from food by barriers preventing migration during expected use must be listed in these regulations, or be the subject of an effective FCN, unless they are authorized elsewhere for the intended use conditions as specified in 21 CFR 177.1395(b)(2) and 21 CFR 177.1390(c)(1). Test protocols presented in Sections 1.A.-H. may be appropriate for evaluating the level of migration from non-food-contact layers of some laminate structures. End uses that differ considerably from those considered in this guidance, however, should be the subject of special protocol development in consultation with FDA.

10. Boil-In-Bags

Use of the protocol for Condition of Use C is recommended.

11. Special High-Temperature Applications

Advances in packaging technology have led to the development of food packaging materials that can withstand temperatures substantially exceeding 121°C (250°F) for short periods of time for the purposes of heating and cooking of ready-prepared food. FDA recommends use of the following protocols for migration testing of dual-ovenable containers, microwavable containers and microwave heat susceptor materials.

a. *DUAL-OVENABLE TRAYS*

For high temperature oven use (conventional and microwave), migration testing should be performed at the maximum intended conventional oven cooking temperature for the longest intended cooking time, using a food oil, or a fatty-food simulant such as Miglyol 812.

b. *MICROWAVABLE CONTAINERS*

The temperature ultimately experienced by a food-contact material when cooking foods in a microwave oven is dependent on many factors. Some of these are food composition, heating time, mass and shape of the food, and shape of the container. For example, food with mass in excess of 5 g/in^2 container surface area and having a thick shape will require longer cooking times to achieve the desired degree of interior cooking than if it had a lower mass-to-surface area ratio and were thinner. Because the ultimate temperature of the container will depend on many factors and, therefore, is not predicted readily, it is recommended that notifiers/petitioners consult with FDA on any planned testing protocol prior to initiating migration testing.

c. *MICROWAVE HEAT-SUSCEPTOR PACKAGING*

The high temperatures attained by packaging using susceptor technology may result in (a) the formation of significant numbers of volatile chemicals from the susceptor components and (b) loss of barrier properties of food-contact materials leading to rapid transfer of nonvolatile adjuvants to foods. Studies by FDA, with hot vegetable oil in contact with a susceptor, have shown that the susceptor materials liberate volatile chemicals that may be retained in the oil at parts-per-billion (ppb) levels. FDA recommends the use of the protocol outlined in an article by McNeal and Hollifield (McNeal and Hollifield, **1993**) for the identification and quantification of *volatiles* from susceptors.

To isolate and identify the total available *nonvolatile* extractives, notifiers/petitioners should perform Soxhlet extractions on finely shredded portions of laminated susceptor materials using polar and nonpolar solvents as outlined in Appendix X1 of ASTM method F1349-91. Migration protocols for *UV-absorbing nonvolatiles* also are outlined in ASTM method F1349-91 and in an article by Begley and Hollifield (Begley and Hollifield, **1991**). The ASTM method relies on the determination of a time-temperature profile based on cooking a food product according to label directions, for the maximum cooking time. The temperature reached by a microwave heat susceptor, however, is dependent on the amount and characteristics of the food product. Testing methods should involve a standard set of conditions that represent the maximum anticipated use conditions. Therefore, FDA recommends that migration studies be conducted in a manner similar to that outlined in the article by Begley and Hollifield. The recommended standard test conditions are as follows:

1) use laminated susceptor stock representative of the proposed application(s);
2) use a microwave oven with an output wattage on the order of 700 watts;
3) use a maximum microwave time of 5 minutes;
4) use an oil mass-to-susceptor surface area on the order of 5 g/in^2; and
5) use a water load on the order of 5 g/in^2.

Exposure estimates may be based, in the absence of validated migration studies, on the assumption of 100% migration of the total nonvolatile extractives to food, as determined by Soxhlet extractions.

Validated migration protocols for the direct determination of aliphatic migrants are not available at this time. However, the amount of aliphatic migrants may be estimated by subtracting the UV-absorbing nonvolatiles and inert materials from the total nonvolatiles obtained by Soxhlet extraction (see Appendix X1 in ASTM method F1349-91). Exposure estimates for aliphatic migrants should be based on the assumption of 100% migration to food.

12. Colorants for Plastics

Some colorants, pigments in particular, may be quite insoluble in the food simulants 10%- and 95%-ethanol. In such cases, solubility information may provide a basis for an alternative to migration testing for evaluating worst-case exposure since migration levels would not be expected to exceed the limits of solubility of the colorant at the proposed use temperature. If the colorant is to be used in all plastic packaging, for which a CF = 0.05 would be used, a solubility below ca. 100 µg/kg at 40°C would lead to a dietary concentration no greater than 5 ppb under conditions as severe as condition of use E. A solubility less than 10 µg/kg would lead to an exposure below the threshold level of 0.5 ppb dietary concentration (see 21 CFR 170.39).

13. Dry Foods with Surface Containing No Free Fat or Oil
(21 CFR 176.170(c), Table 1, Food Type VIII)

Although studies have shown migration of certain adjuvants into dry foods (e.g., low molecular weight adjuvants in contact with porous or powdered foods), at the present time no migration testing is recommended.

14. Wet-End Additives used in the Manufacture of Paper and Paperboard

Paper additives used in the wet-end of papermaking include those designed to improve the papermaking process, such as processing aids, and those designed to modify the properties of the paper, such as functional aids. Functional aids, mostly organic resins or inorganic fillers, are designed to bond to the paper fibers and, thus, are substantive to paper. For those FCSs that are substantive to paper, migration studies should be conducted and the test solutions analyzed for constituents of the substance. For example, in the case of a polymeric retention aid, the test solutions should be analyzed for constituent oligomers and monomers. On the other hand, processing aids are intended to remain with the process water slurry and, thus, are generally not substantive to paper. Exposure estimates for non-substantive additives may be based on migration studies, or alternatively, on scenarios involving partitioning of the additive between paper fibers and slurry water. The following example illustrates this approach:

Consider an adjuvant added prior to the sheet-forming operation in the manufacture of paper. The intended use level is reported to be 10 mg/kg in the slurry. Since the additive is not substantive to paper, the mass of water (containing the additive) in contact with the pulp at the point in the papermaking process where the slurry enters the drier determines the level of the adjuvant retained in paper. Prior to entering the driers, the slurry is mechanically concentrated to contain approximately 33% pulp and 67% water. This corresponds to an adjuvant level of 20 mg/kg relative to the pulp. Assuming that finished paper contains 92% pulp, a paper basis weight of 50 mg/in^2, 100% migration of the adjuvant to food, and that 10 g of food contacts 1 in^2 paper, this results in an adjuvant concentration in food of 0.09 mg/kg, or 90 µg/kg. Applying a CF of 0.1 for uncoated and clay-coated paper gives a dietary concentration of 9 ppb.

15. Materials for use during the Irradiation of Prepackaged Food

    For materials that will be subjected to incidental ionizing radiation through irradiation of pre-packaged food, consult with OFAS for special migration study protocols.

APPENDIX III.

ILLUSTRATIVE EXAMPLE OF VALIDATION OF ANALYSES

Polyethylene film containing a new antioxidant was subjected to migration testing with 10% ethanol. The test solutions were analyzed for antioxidant migration. Tests were carried out in separate cells each containing 100 in^2 of film. Four sets of test solutions (in triplicate) were analyzed at 2, 24, 96 and 240 hours for a total of 12 test solutions. After each time interval, each solution from one set was evaporated to dryness, the residue dissolved in an appropriate organic solvent, and a known aliquot injected into a gas chromatograph.

Validation experiments are carried out with the set of test simulants exhibiting the highest level of antioxidant migration. To validate the analytical method, an additional three sets (in triplicate) using 10% ethanol can be run for 240 hours. Each set of these test solutions then can be fortified with the antioxidant at levels corresponding to one-half (1/2), one (1) and two (2) times, respectively, the average migration value determined for the regular (unfortified) 240 hour test solutions.

Instead, the notifier/petitioner decided to carry out one large test using enough film and solvent for twelve analyses (three at each of the four time intervals). After 240 hours, the test solution was divided into twelve (12) equal solutions (i.e., four sets of triplicate samples). One set (three solutions) was found to contain antioxidant at an average level of 0.00080 mg/in^2. This value corresponds to 0.080 mg/kg in food if it is assumed that 10 grams of food contacts 1 in^2 of film. Of the remaining nine solutions (three sets), three solutions were fortified at concentrations corresponding to 0.00040 mg/in^2, three were fortified at 0.00080 mg/in^2, and three were fortified at 0.00160 mg/in^2. Each solution was worked up and analyzed as described above. To illustrate the recovery calculations, the results for the set of three solutions fortified at one-half times the average migration (0.00040 mg/in^2) are summarized in the following table:

Measured Level in each Sample (mg/in^2)[(a)]	Recovery (mg/in^2)[(b)]	Percent Recovery (%)[(c)]
0.00110	0.00030	75.0
0.00105	0.00025	62.5
0.00112	0.00032	85.0

[(a)]includes 0.00040 mg/in^2 fortification.
[(b)]calculated by subtracting the average level (0.00080 mg/in^2) from the measured levels in each sample.
[(c)]calculated by dividing the recovery by the fortification level (0.00040 mg/in^2), and multiplying by 100 (see Section II.D.3.e.).

The average percent recovery is 74.2%, and the relative standard deviation is 15.2%. These are within the limits specified (see Section II.D.3.e.) for a concentration in food of 0.080 mg/kg (percent recovery 60-110%, relative standard deviation not exceeding 20%). If the corresponding percentages for the other two fortification levels are also within these limits, the validation for the 10% ethanol migration studies would be acceptable. The actual validation procedure used will, of course, depend on the particular type of analysis.

APPENDIX IV.

CONSUMPTION FACTORS, FOOD-TYPE DISTRIBUTION FACTORS, AND EXAMPLE OF EXPOSURE ESTIMATE CALCULATIONS

This appendix summarizes packaging data recommended by FDA for evaluating exposure to FCS. An example of how these data are combined with levels of an FCS in food also is presented. A more complete discussion of the source of these data and their use in exposure calculations is presented in Section II.E.

TABLE I - CONSUMPTION FACTORS (CF)

Package Category	CF	Package Category	CF
A. General			
Glass	0.1	Adhesives	0.14
Metal- Polymer coated	0.17	Retort pouch	0.05
Metal- Uncoated	0.03	Microwave susceptor	0.001
Paper- Polymer coated	0.2		
Paper- Uncoated and clay-coated	0.1		
Polymer	0.4		
B. Polymer			
Polyolefins	0.35	PVC	0.1
-LDPE	0.12	-rigid/semirigid	0.05
-LLDPE	0.06	-plasticized	0.05
-HDPE	0.13	PET[(a)]	0.16
-PP	0.04	Other Polyesters	0.05
Polystyrene	0.1	Cellophane	0.01
-impact	0.04	Nylon	0.02

-non-impact	0.06[b]	Acrylics, phenolics, *etc.*	0.15
EVA	0.02	All Others[c]	0.05

[a] A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").
[b] General purpose, 0.02; foam, 0.04
[c] As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

TABLE II - FOOD-TYPE DISTRIBUTION FACTORS (f_T)

Package Category	**Food-Type Distribution (f_T)**			
	Aqueous[a]	**Acidic[a]**	**Alcoholic**	**Fatty**
A. General				
Glass	0.08	0.36	0.47	0.09
Metal- Polymer coated	0.16	0.35	0.40	0.09
Metal- Uncoated	0.54	0.25	0.01[b]	0.20
Paper- Polymer coated	0.55	0.04	0.01[b]	0.40
Paper- Uncoated and clay-coated	0.57	0.01[b]	0.01[b]	0.41
Polymer	0.49	0.16	0.01[b]	0.34
B. Polymer				
Polyolefins	0.67	0.01[b]	0.01[b]	0.31
Polystyrene	0.67	0.01[b]	0.01[b]	0.31
-impact	0.85	0.01[b]	0.04	0.10
-nonimpact	0.51	0.01	0.01	0.47
Acrylics, phenolics, *etc.*	0.17	0.40	0.31	0.12
PVC	0.01[b]	0.23	0.27	0.49
Polyacrylonitrile, ionomers, PVDC	0.01[b]	0.01[b]	0.01[b]	0.97

Polycarbonates	0.97	0.01[b]	0.01[b]	0.01[b]
Polyesters	0.01[b]	0.97	0.01[b]	0.01[b]
Polyamides (nylons)	0.10	0.10	0.05	0.75
EVA	0.30	0.28	0.28	0.14
Wax	0.47	0.01[b]	0.01[b]	0.51
Cellophane	0.05	0.01[b]	0.01[b]	0.93

[a]For 10% ethanol as the food simulant for aqueous and acidic foods, the food-type distribution factors should be summed.
[b]1% or less

Examples of Exposure Estimate Calculations

The following hypothetical examples are intended to illustrate the calculation of the concentration of an FCS in the daily diet (CF x <M>, i.e., the fraction of food in the diet contacting the food-contact article times the average concentration of the FCS in food) and its EDI and CEDI.

Example 1

An FCN is received that describes the use of a new antioxidant at a maximum level of 0.25% w/w in polyolefins contacting food at or below room temperature (see Appendix II. Sections 1.E. through 1.G.). Migration values from LDPE reported to FDA for the three food simulants are given below:

Solvent (i)	M_i (mg/kg)
10% aqueous ethanol	0.060
50% aqueous ethanol	0.092
Miglyol 812	7.7

The notifier used a solvent volume-to-exposed surface area ratio of 10 mL/in^2. Therefore, solution concentrations are essentially equivalent to food concentrations (under the assumption that 10 g food contacts 1 in^2 of surface area). The CF and f_Ts for polyolefins are given in Tables I and II, respectively. The <M> for the antioxidant would be calculated as follows:

$$\langle M \rangle = (f_{aqueous}+f_{acidic})(M_{10\%\ Ethanol}) + f_{alcohol}(M_{50\%\ Ethanol}) + f_{fatty}(M_{Miglyol\ 812})$$

$$= 0.68(0.060\ mg/kg)+0.01(0.092\ mg/kg)+0.31(7.7\ mg/kg)$$

$$= 2.4\ mg/kg$$

The concentration of the antioxidant in the daily diet resulting from the proposed use would be:

CF x <M> = 0.35 x 2.4 mg/kg

= 0.84 mg/kg

If there were no other permitted uses, then the CEDI would be calculated using the above value:

CEDI = 3 kg food/person/day x 0.84 mg antioxidant/kg food

= 2.5 mg/person/day

Example 2

In a subsequent notification, expanded use of the same antioxidant in polycarbonate and polystyrene food contact articles is described. Each polymer would contact food at or below room temperature. Migration levels are given below:

Solvent	**Migration to Food (mg/kg)**		
	Polycarbonate	**Polystyrene**	**Impact Polystyrene**
10% aq. ethanol	0.020	0.020	0.020
50% aq. ethanol	0.025	0.035	0.22
Miglyol 812	0.033	0.15	6.2

The concentration of the antioxidant in the daily diet resulting from each of the proposed uses is calculated below. A CF of 0.04 for impact polystyrene and a CF of 0.06 for all other polystyrenes was used in the calculation.

Polycarbonates

CF x <M> = 0.05(0.98(0.020 mg/kg) +0.01(0.025 mg/kg)+0.01(0.033 mg/kg))

= 0.001 mg/kg

Polystyrene

CF x <M> = 0.06(0.52(0.020 mg/kg) +0.01(0.035 mg/kg)+0.47(0.15 mg/kg))

= 0.0049 mg/kg

Impact Polystyrene

CF x <M> = 0.04(0.86(0.020 mg/kg) +0.04(0.22 mg/kg)+0.10(6.2 mg/kg))

= 0.026 mg/kg

The total concentration of the antioxidant in the daily diet resulting from the additional uses in polycarbonate and polystyrene is approximately 0.032 mg/kg.

The contribution to the EDI is:

EDI = 3 kg food/person/day x 0.032 mg antioxidant/kg food

= 0.096 mg/person/day

The CEDI for the previously permitted use (Example 1, EDI of 2.5 mg/person/day) and the additional proposed uses (EDI of 0.1 mg/person/day) would be 2.6 mg/person/day.

APPENDIX V.

REFERENCES

General References

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Arthur D. Little, Inc., July **1983**: A Study of Indirect Food Additive Migration. Final Summary Report. 223-77-2360.

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Arthur D. Little, Inc., August **1990**: High Temperature Migration Testing of Indirect Food Additives to Food. Final Report. FDA Contract No. 223-89-2202.

ASTM E 1511-95, Standard Practice for Testing Conductivity Detectors Used in Liquid or Ion Chromatography. ASTM, West Conshohocken, PA 19428-2959.

Baner, A., Brandsch, J., Franz, R. and Piringer, O., **1996**, The Application of a predictive migration model for evaluating the compliance of plastic materials with European food regulations. *Food Additives and Contaminants*, **13** (5), 587-601.

Begley, T. H. and Hollifield, H. C., **1991**, Application of a polytetrafluoroethylene single-sided migration cell for measuring migration through microwave susceptor films.*American Chemical Society Symposium Series 473: Food and Packaging Interactions II*, Chapter **5**, 53-66.

Chang, S., **1984**, Migration of low molecular weight components from polymers: 1. Methodology and

diffusion of straight-chain octadecane in polyolefins. *Polymer*, **25**, 209-217.

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McNeal, T. P. and Hollifield, H. C., **1993**, Determination of volatile chemicals released from microwave-heat-susceptor food packaging. *J. AOAC International*, **76** (6), 1268-1275.

National Bureau of Standards, March **1982**: Migration of Low Molecular Weight Additives in Polyolefins and Copolymers. Final Project Report, NBSIR 82-2472. NTIS PB 82-196403, National Technical Information Services, Springfield, VA.

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Schwope, A. D., Till, D. E., Ehntholt, D. J., Sidman, K. R., Whelan, R. H., Schwartz, P. S., and Reid, R. C., **1987**, Migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. *Food and Chemical Toxicology*, **25** (4), 317-326.

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The following are lists of references that contain descriptions, photos, or drawings of migration cells for conducting migration testing for different packaging applications.

Cells for Migration Testing

Conventional Applications

ASTM F34-98, Standard Practice for Construction of Test Cell for Liquid Extraction of Barrier Materials. ASTM, West Conshohocken, PA 19428-2959.

Dow Chemical, Inc., A single-sided migration cell, known as the Dow cell, has been used with food oil at 175°C. The cell is available from: Kayeness, Inc., 115 Thousand Oaks Blvd., Suite 101, P.O. Box 709, Morgantown, PA 19543 (610-286-7555). Model no. D9030.

Figge, K. and Koch, J., **1973**, Effect of some variables on the migration of additives from plastics into edible fats. *Food Cosmetics Toxicology*, **11**, 975-988. The cell used was a single-sided cell in contact with food oil at 80°C.

Goydan, R., Schwope, A. D., Reid, R. C., and Cramer, G., **1990**. The cell used was a double-sided (immersion), stainless steel cell, with water, 95% ethanol, and oil at 130°C.

Limm, W. and Hollifield, H., **1995**. The cell used was a single-sided glass cell with water, food oil, and food at 135°C.

Snyder, R.C. and Breder, C.V., **1985**. The cell used was a double-sided (immersion) glass cell with water, 3% acetic acid, 95% ethanol, and oil at 40°C and 50% aqueous ethanol at 70°C. This cell is also specified in ASTM D4754-87 "Standard Test Method for the Two-Sided Liquid Extraction of Plastic Materials Using FDA Migration Cell." ASTM, West Conshohocken, PA 19428-2959.

Till, D.E., Ehntholt, D. J., Reid, R. C., Schwartz, P. S., Sidman, K. R., Schwope, A. D., and Whelan, R. H., **1982**. The cells used were glass, single-sided and double-sided (immersion) cells, with water, 3% acetic acid, 95% ethanol, and oil at 40°C.

Microwave Applications

ASTM F1349-91, Standard Test Method for Nonvolatile Ultraviolet (UV) Absorbing Extractables from Microwave Susceptors. ASTM, West Conshohocken, PA 19428-2959.

Begley, T. and Hollifield, H., **1991**. The cell was used with food oil at temperatures up to 240°C.

Rijk, R. and De Kruijf, N., **1993**, Migration testing with olive oil in a microwave oven. *Food Additives and Contaminants*, **10** (6), 631-645.

Footnotes

1. CAS Registry Numbers for new compounds and assistance with nomenclature can be obtained by writing to Chemical Abstracts Service (CAS) Client Services, 2540 Olentangy River Road, P.O. Box 3343, Columbus, OH 43210, or by visiting their website at http://www.cas.org/.

2. Migration into food depends on the chemical structure of the FCS, the nature of the food matrix contacting the FCS, the type of food with which it is in contact, and the temperature and duration of food contact. Prior to the submission of an FCN or FAP, a potential submitter may wish to meet or correspond with FDA to discuss appropriate migration testing protocols (see Section III.).

3. Migration values often are expressed in units of mg/dm^2. The mixed unit, mg/in^2, is preferred, however, to facilitate conversion to concentrations in food. If 10 g of food are in contact with 1 square inch of food-contact surface, a migration of 0.010 mg/in^2 corresponds to a concentration in food of 1 mg/kg.

4. In the past, FDA recommended 8% ethanol as an aqueous food simulant. Increasing the ethanol concentration from 8% to 10% will have a minimal impact on migration studies conducted on adjuvant/polymer systems. This change also harmonizes more closely FDA's migration protocols with those of other nations. See the reference list at the end of Appendix II. relating to FDA's development of the use of food simulants.

5. Miglyol 812, a product of Dynamit Nobel Chemicals, is available from HULS America, Inc., 80 Centennial Ave., P. O. Box 456, Piscataway, NJ 08855-0456.

6. HB307 is available from NATEC, Behringstrasse 154, Postfach 501568, 2000 Hamburg 50, Germany.

7. Previous test protocols (prior to 1995) recommended a test temperature of 49°C for 10 days. Recent studies by FDA, however, have shown little difference in migration levels at 49°C and 40°C (104°F). Furthermore, the differences in migration levels between 49°C and 40°C are of even less significance for migration studies requiring elevated temperatures (*e.g.*, 100°C or 121°C) for the first two hours. Up to 80% of the total migration observed over the 10 day period is usually completed within this two hour period at the higher temperature. Therefore, 40°C is acceptable for migration studies for room-temperature applications and for the portion of the migration test for elevated-temperature applications intended to reflect long term ambient storage.

8. The LOD is the lowest concentration of analyte that the analytical method can reliably detect above a blank (or control). It is preferable that the LOD be determined from analyses of five blank samples. The blank signal (*i.e.*, the analyte response for the blank sample or the width of the baseline close to the actual or expected analyte peak) is measured, and the average signal and standard deviation for the blank are calculated. The signal corresponding to the LOD is located three standard deviations above the average blank signal. The blank signal for the LOD is usually determined from the peak-to-peak noise measured on the baseline close to the actual or expected analyte signal. See American Society for Testing and Materials (ASTM), E 1303-95 or ASTM E 1511-95.

The region for quantitation of the analyte should clearly be above the LOD. The signal corresponding to the LOQ is located ten standard deviations above the average blank signal. See (Currie, **1968**) and

(Keith., et al, **1980**).

Food Additives and Premarket Approval

Content last updated by abb/def/mac/msl on 2002-FEB-04
Hypertext last updated by mac/msl/emw 2002-MAR-06

TOX GUIDANCE

U. S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
March, 2002

Guidance for Industry

Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations

FINAL GUIDANCE

March 2002

Comments and suggestions regarding this document may be submitted at any time. Submit Comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD, 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register (Docket No: 99D-4576).

For questions on the content of the document contact the Office of Food Additive Safety (OFAS), Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), 5100 Paint Branch Parkway, College Park, Maryland 20740-3835, (Tel) 202-418-3087.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition (CFSAN)
March 2002

HIGHLIGHTS OF TOXICOLOGY RECOMMENDATIONS IN THE 2002 GUIDANCE

- **Safety Summary and Comprehensive Toxicological Profile (CTP).** The safety information for a food contact notification (FCN) should contain both a safety summary and a comprehensive toxicological profile (CTP) of the food contact substance (FCS) that is the subject of the notification. The safety summary is Part III of FDA Form 3480 and should provide the basis for the notifier's determination that the intended use of the FCS is safe. The CTP should provide summaries of all the available toxicological information pertinent to the safety evaluation of the FCS. In some cases, a notification may need to include a CTP for a toxicologically relevant constituent of the FCS. If a constituent of an FCS is carcinogenic, the CTP in the notification should include a quantitative risk assessment.

- **Safety Testing Recommendations for Food Contact Substances (FCSs) and Their Constituents.** This document recommends safety testing of FCSs and their constituents, primarily based on a series of genetic toxicity tests and, when justified by the exposure level, subchronic

toxicity studies. The recommendations describe the minimum level of safety testing generally considered appropriate at various exposures. For an initial or incremental exposure of an FCS at or less than 0.5 parts per billion (ppb), no safety tests are recommended. For a cumulative exposure between 0.5 ppb and 1 part per million (ppm), genetic toxicity tests and/or subchronic tests are recommended. At a cumulative exposure at or greater than 1 ppm, FDA normally requires, under the authority of Section 409 (h)(3)(B) of the Federal Food, Drug and Cosmetic Act, that a food additive petition be submitted for the use of an FCS.

- **Evaluation of Structural Similarities to Known Toxicants.** To the extent feasible, knowledge in predicting potential toxicity based on structure/activity relationships may be incorporated into the safety assessment of an FCS. Such information may be used as part of an overall strategy for assessing the safety of an FCS or to help interpret safety test results.

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Guidance for Industry

Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations

FINAL GUIDANCE

This guidance represents FDA's current thinking on the Toxicology Recommendations for preparation of Food Contact Substances. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of applicable statutes and regulations. This guidance is being issued in accordance with FDA's Good Guidance Practices (21 CFR 10.115).

I. INTRODUCTION

Section 309 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended Section 409 of the Federal Food, Drug and Cosmetic Act (the Act) to establish a food contact notification process as the primary means by which the Food and Drug Administration (FDA) regulates food additives that are food contact substances (FCSs). An FCS is any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if the use is not intended to have any technical effect in the food (sec. 409(h)(6) of the Act).

An FCS that is a food additive must be regulated for its intended use in 21 CFR Parts 173-178, be exempted from regulation under the Agency's Threshold of Regulation Policy (21 CFR 170.39), or be the subject of a notification under section 409(h) of the Act that is effective (sec. 409(a)(3) of the Act). Both FCNs and food additive petitions (FAPs) for FCSs must contain sufficient scientific information to demonstrate that the substance that is the subject of the notification or petition is safe for the intended use (secs. 409(h)(1) and 409(b) of the Act). Section 409(b) of the Act sets forth the statutory requirements for data in a FAP to establish the safety of a food additive. These requirements include full reports of investigations made with respect to the safety of the additive. Because the safety standard is the same for all food additives, whether subject to the FCN process or the petition process, the data and information that should be included in an FCN or FAP are comparable.

II. EXPOSURE ESTIMATES

The level of safety testing that is recommended to support an FCN for an FCS is largely determined by the cumulative estimated daily intake (CEDI) of the FCS. The CEDI is the sum of the estimated daily intakes (EDIs) of the FCS that may result from the application of the substance described in the notification and any other regulated food uses of the substance. For information on estimating human dietary exposures, refer to the document entitled "Guidance for Industry: Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations."

In some cases, limitations in the submitted chemistry information could affect the magnitude of an exposure estimate, and thereby affect the toxicological testing recommendations. Therefore, FDA recommends that a notifier provide adequate information on the level of the FCS expected in foods in order for an estimate of the CEDI to reflect probable consumer exposure to the FCS and to ensure that the appropriate level of safety testing is conducted.

FDA recognizes that the use of CEDI in this guidance appears to differ from the approach of FDA's Threshold of Regulation (TOR) process (21 CFR 170.39). The two approaches are, in fact, consistent. Under TOR, indirect food additive uses that result in incremental exposures at or less than 0.5 ppb in the diet are eligible for exemption from the food additive petition requirement. At the time the TOR process was established, FDA determined that, because of the conservative assumptions ordinarily applied in estimating exposure, the cumulative exposure from a limited number of trivial food additive uses is not likely to be more than negligible. Accordingly, in the case of the TOR exposure levels, it was not necessary to utilize cumulative exposure levels. FDA believes that the determination made in establishing its TOR is still sound.

III. TEST SUBSTANCE

FDA generally recommends that the test substance for safety studies be identical to the substance that is expected to migrate to food. Ordinarily, the appropriate test substance is the FCS itself. In some cases, however, appropriate test substances may include various constituents of the FCS, such as minor components, materials used in manufacturing, or decomposition products, if these constituents are expected to migrate to food. For example, for an FCS that is a polymer, FDA recommends testing low-molecular weight oligomers for toxicity, but not the polymer itself, as the oligomers may be expected to be the primary migrant to food from the FCS.

Some FCSs decompose to other substances that exert technical effects either during the manufacture of food contact materials (e.g., slimicides) or in food contact materials themselves (e.g., phosphorus-based antioxidants in which phosphorus oxidizes to phosphates and phosphites). Other FCSs decompose as a consequence of imparting their technical effect or are known to decompose during processing, in storage, and in food or food-simulating solvents (e.g., antioxidants in polymers). In such cases, decomposition products of the FCSs may be appropriate test substances for safety studies.

Test and control substances used in the safety studies should be characterized and handled in accordance with the Good Laboratory Practice regulations for non-clinical laboratory studies (21 CFR Part 58, Subpart F - Test and Control Articles). In all cases, the composition of the test substance used in safety studies should be known. Notifiers should provide the names, structural formulae, and quantities of major components and other constituents of the test substance, and the approximate total quantity of unidentified material. If available, both common names and trade names should be provided. A single batch of a test substance should be used for a safety study, if possible. If more than one batch is used, the strength, composition, purity, and other characteristics of each batch should be approximately the same.

Additional information on the chemical identity of the FCS and its constituents is contained in the document "Guidance for Industry: Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations." For guidance on safety studies for specific test substances, notifiers are advised to contact FDA.

IV. SAFETY TESTING RECOMMENDATIONS

A. Minimum Testing Recommendations

FDA recommends studies to assess the safety of an FCS and its constituent(s) if appropriate, on the basis of the CEDI (see II). These recommendations are consistent with the general principle that the potential risk of a substance is likely to increase as exposure increases.

FDA recommends that notifiers submit, as a minimum, the following studies and other information to assess the safety of an FCS (and each constituent as appropriate):

1. Incremental exposure at or less than 0.5 ppb (*i.e.*, 1.5 ug/person/day) in the diet

    a. No safety studies are recommended for an FCS (or a constituent, as appropriate) if exposure for a single use is at or less than 0.5 ppb.

    b. Available information on the potential carcinogenicity of such substances should be discussed in a CTP (*e.g.*, carcinogenicity studies, genetic toxicity

studies, or information on structural similarity to known mutagens or carcinogens (see IX)).

c. For a carcinogenic constituent of an FCS, the CTP should contain an estimate of the potential human cancer risk from the constituent due to the proposed use of the FCS (see VII. C.).

2. Cumulative exposure greater than 0.5 ppb (i.e., 1.5 ug/person/day) but not exceeding 50 ppb (*i.e.*, 150 ug/person/day)

   a. The potential carcinogenicity of an FCS (and/or a constituent, if appropriate) with a cumulative exposure between 0.5 ppb and 50 ppb should be evaluated using genetic toxicity tests. The recommended genetic toxicity tests include: (1) a test for gene mutations in bacteria and (2) an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells or an *in vitro* mouse lymphoma $tk^{+/-}$ assay. FDA prefers the mouse lymphoma $tk^{+/-}k$ assay because this assay measures heritable genetic damage in living cells and is capable of detecting chemicals that induce either gene mutations or chromosomal aberrations, including genetic events associated with carcinogenesis. In performing the mouse lymphoma $tk^{+/-}$ assay, either the soft agar or the microwell method should be used.

   b. Additional information on the potential carcinogenicity of such a substance should be discussed, as appropriate, in CTPs (e.g. carcinogenicity studies, genetic toxicity studies, information on structural similarity to known mutagens and carcinogens (see IX), etc.).

   c. For a carcinogenic constituent of an FCS, the CTP should estimate the potential human cancer risk from the constituent due to the proposed use of the FCS (see VII.C.).

3. Cumulative exposure between 50 ppb (i.e., 150 ug/person/day) and 1 part per million (ppm) (*i.e.*, 3 mg/person/day)

   a. The potential carcinogenicity of an FCS (and/or a constituent, if appropriate) with an estimated cumulative exposure between 50 ppb and 1 ppm should be evaluated using genetic toxicity tests. The recommended genetic toxicity tests include: (1) a test for gene mutations in bacteria; (2) an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells *or* an *in vitro* mouse lymphoma $tk^{+/-}$ assay (the mouse lymphoma assay is preferred); and, (3) an *in vivo* test for chromosomal damage using rodent hematopoietic cells. In performing the mouse lymphoma $tk^{+/-}$ assay, either the soft agar or the microwell method should be used.

   b. Additional information on the potential carcinogenicity of such a substance should be discussed, as appropriate, in CTPs (*e.g.*, carcinogenicity studies, genetic toxicity studies, information on structural similarity to known mutagens or carcinogens (see IX), etc.).

c. For a carcinogenic constituent of an FCS, the CTP should estimate the potential human risk from the constituent due to the proposed use of the FCS (see VII.C.).

d. The potential toxicity of an FCS (and/or a constituent, if appropriate) should be evaluated by two subchronic oral toxicity tests, one in a rodent species and one in a non-rodent species. The studies should provide an adequate basis for determining an acceptable daily intake (ADI) for the FCS or a constituent in the indicated range of CEDIs. In addition, the results of these studies will help determine whether longer-term or specialized safety tests (*e.g.*, metabolism studies, teratogenicity studies, reproductive toxicity studies, neurotoxicity studies, and immunotoxicity studies) should be conducted to assess the safety of these substances.

4. Cumulative exposure at or greater than 1 ppm (*i.e.*, 3 mg/person/day)

   When the estimated exposure to an FCS or a constituent is 1 ppm or greater, FDA recommends that a food additive petition be submitted for the FCS (see XI).

B. Safety Testing Protocols

Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (FDA, 1982) provides general guidance on the conduct of standard toxicity tests, other than genetic toxicology tests, and it is relevant to toxicity testing of FCSs and their constituents. Additional information may also be found in the 1993 draft of Redbook II. As sections of the 1993 draft of Redbook are revised in response to comments, they are being made available on the internet at http://www.cfsan.fda.gov/~redbook/red-toca.html (FDA, 2000).

The Redbook sections available on FDA's internet site (http://www.cfsan.fda.gov)include guidelines on the conduct of certain genetic toxicity tests. For genetic toxicity tests not yet found on this website, FDA recommends that notifiers consult the testing guidelines published by the Organization for Economic Co-operation and Development (OECD) or the guidelines of the United States Environmental Protection Agency (EPA) and the genotoxicity guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Alternative procedures for conducting safety tests may be used. In such cases, FDA recommends that notifiers consult with scientists at FDA on proposed deviations from recommended safety test protocols before the tests are conducted.

All safety studies should be conducted according to the good laboratory practice (GLP) regulations of the Food and Drug Administration, or the GLP guidelines of the United States Environmental Protection Agency, or the OECD. If a study was not conducted in compliance with the regulations or guidelines, a brief statement of the reason for noncompliance should be given. For a safety study conducted after 1978 that does not comply with FDA GLP regulations, FDA has proposed to require that notifiers include a report of a data audit by an independent third party auditor if the study is pivotal to assessing the safety of the FCS.

C. Application of the Testing Recommendations to Biocides

Biocides are a class of FCSs that are toxic by design. Consequently, FDA recommends that notifiers apply FDA's minimum testing recommendations (see IV.A.) to biocides at CEDIs that are 1/5 the value of the CEDIs used to determine the appropriate level of safety testing for other types of FCSs. FDA considers these lower exposure cutoffs appropriate for FCSs used primarily for their antimicrobial or fungicidal effects.

D. Genetic Toxicity Testing Recommendations

For an FCS with a cumulative exposure greater than 0.5 ppb, FDA recommends that genetic toxicity testing be done. This is because carcinogenicity is an ongoing health concern at low levels of exposure and genetic toxicity testing is the most reliable experimental indicator of potential carcinogenicity, with the exception of full-scale chronic animal carcinogenicity studies.

In some cases, genetic toxicity testing may not be useful, or the recommendations that are provided above may need to be modified. For example, FDA believes that genetic toxicity testing of polymers is unnecessary, and that testing of oligomers and other constituents that can migrate into foods is more appropriate.

E. Flexibility in Applying FDA's Recommendations

The information and guidance provided in this document are intended to help ensure that sufficient safety information is available on an FCS and its constituent(s) to determine whether the substance is safe under its intended conditions of use. Although the information contained in this document represents FDA's current thinking on the safety information needed to establish the safety of an FCS and its constituents, an alternative approach may be used by a notifier if the approach satisfies the applicable statute and regulations.

The guidance discussed in this document permits notifiers to exercise their own judgment in selecting safety tests to be performed for FCSs. The level of testing and types of safety information needed for determining the safety of a particular FCS or its constituent(s) should be evaluated on a case-by-case basis. Intended use, potential acute and chronic toxicity (e.g., signs/symptoms of neurotoxicity and hyperplasia, respectively), and structural alerts are some of the factors that should be considered.

V. ORGANIZATION OF THE SAFETY INFORMATION

FDA recommends that the notifier organize the safety information into two parts. The first part of the safety information should be provided in Part III of FDA Form 3480. The second part of the safety information is the safety data package attached to FDA Form 3480.

Part III of FDA Form 3480 is the safety summary. The safety summary in Part III of FDA Form 3480 is divided into four sections: Section A- the safety narrative, Section B- a tabulation of relevant safety studies on the food contact substance (FCS), Section C- a tabulation of information about the potential carcinogenicity and toxicity of constituent(s), and Section D- a brief description of any other relevant information not included in the other sections. Detailed information on preparing the safety narrative (SN) (Section A of FDA Form 3480) is provided in

this guidance document (see VI).

The second part of the safety information in the notification is the safety data package. FDA recommends that the notifier organize the safety data package as follows:

- Section I. Comprehensive Toxicology Profile(s)
- Section II. Original Reports of Safety Studies
- Section III. Published literature
- Section IV. Appendices

Detailed information for preparing the comprehensive toxicology profile(s) (Section I of safety data package) is provided in this guidance document (see VII).

Sections II of the safety data package should contain the original reports of safety studies and Section III should contain the published literature (*i.e.*, data or information that the notifier relied upon to prepare Section I). When available, full study reports, including the primary data (*i.e.*, individual animal data, plate counts, etc.), should be submitted for all of the recommended safety studies, cancer bioassays, and other pivotal studies on the FCS and its constituents, as appropriate. The original study reports should be included in the safety data package whether conducted by the notifier or by a third party. It is particularly important that notifiers submit full study reports of studies and related information that are used quantitatively, for example, to conduct risk assessments or set no-observed-effect levels. For clarification or to determine if the full study report for a specific safety study should be included in an FCN notifiers are advised to contact FDA.

Section IV of the safety data package should include appendices with data and other information not addressed in other sections of the safety data package. Such data typically would have been considered by the notifier and judged to be supplementary. The inclusion of such information in this section is intended to permit FDA to make an independent assessment of the utility of such information. In particular, FDA recommends that notifiers include abstracts of available studies not discussed in the CTP in this section with a statement regarding the notifier's rationale for their exclusion. If such studies and information are voluminous, FDA recommends that the notifier contact FDA before preparing such an appendix. In addition, the appendix should include the results of all literature searches conducted and information relevant to the searches (*e.g.*, names of selected databases, the period of years searched, the specific search terms used, etc.) under a separate heading. Other information in Section IV might include material safety data sheets, book chapters, review articles, etc.

VI. SAFETY NARRATIVE (SN)

Each notification should contain a safety narrative (SN). A SN is a concise summary of the scientific basis for a safety decision. Ordinarily, the SN should reference the estimated human exposure and potential toxicity of the FCS and its constituent(s), and should be based on chemistry and safety information and analyses described in detail in other sections of the notification. In the SN, the notifier should be explicit in reporting all effects of an FCS, including those considered adverse or physiologic. The SN should also include conclusions regarding the mutagenic and carcinogenic potential of the FCS and any toxicologically relevant constituents, as

appropriate. Furthermore, the SN should provide the appropriate worst-case, upper-bound, lifetime risk levels for carcinogenic constituents associated with the FCS. However, a detailed quantitative risk assessment procedure for carcinogenic constituents of FCSs is not needed in this section. (See VII.C.) If an ADI for the FCS is determined, it should be justified in terms of the most relevant study and end-point chosen, the animal species selected, and the safety (or uncertainty) factor applied. Generally, an ADI for an FCS with a CEDI below 50 ppb is not available. In cases where appropriate studies are available, an ADI may be calculated. If a previously established ADI supports the new intended use of an FCS, this should be discussed.

To calculate an ADI, the no-observed-effect level (NOEL) for each identified adverse effect from all relevant safety studies should be multiplied by an appropriate safety factor. Information on determining the NOEL is given in Section VII.B of this guidance document. In general, FDA recommends that the notifier use a safety factor of 1/1000 if NOELs are derived from subchronic studies and 1/100 for NOELs derived from chronic studies. For reproduction and developmental endpoints, FDA recommends that the notifier use a safety factor of 1/1000 if the observed effects are severe or irreversible (*e.g.*, a missing limb or decrease in the number of pups born live); otherwise, FDA recommends a safety factor of 1/100. Additional adjustments may be appropriate when considered on a case-by-case basis.

Traditionally, the lowest ADI would be chosen as the definitive ADI, unless there is scientific rationale not to do so (*e.g.*, if a toxicological effect seen in animals is shown not to occur in humans).

VII. COMPREHENSIVE TOXICOLOGICAL PROFILE (CTP)

Each notification should include a CTP of all unpublished and published safety studies and related information relevant to the safety assessment of the FCS. If there are constituent(s) of the FCS that are expected to migrate to food, then a CTP for each constituent of potential toxicological concern should also be provided in the notification.

In preparing a CTP, all safety studies that identify adverse effects of the substance or that bear significantly on the determination of an ADI for the substance should be addressed. FDA's views on the relevance, in general, of various types of safety studies are discussed below (see VIII) and should be considered in preparing the CTP.

If the test substance in a specific study that is addressed in the CTP differs from the FCS, its relationship to the FCS should be clearly indicated. For example, the test substance should be identified as a constituent of the FCS (e.g., monomer, oligomer, decomposition product, side reaction product or impurity, as appropriate).

FDA's recommendations on preparing key components of the CTP, including study summaries, determination of NOELs, risk assessments, and bibliography are provided below.

A. Preparation of Study Summaries for the CTP

1. Study Summaries for Genetic Toxicity Studies

The potential for genetic toxicity is an important consideration in the safety evaluation of FCSs. Information on the genetic toxicity of the FCS and its constituents should be described in detail in the CTPs. In evaluating the safety of the

FCS and its constituents, notifiers should consider all published and unpublished genetic toxicity data.

In summarizing genetic toxicity studies, FDA recommends that the notifier:

- Group the available data by test systems (e.g., gene mutations in bacteria, gene mutations in cultured mammalian cells, chromosomal aberrations in vitro, chromosomal aberrations in vivo, etc.). Individual studies within the same test system should be presented in chronological order.
- Prepare a table of the genetic toxicity data for the FCS and its constituents if appropriate.
- Formulate and justify an overall conclusion regarding the genotoxic potential of the FCS and its constituents if appropriate.

2. Study Summaries for *in vivo* Toxicity Tests

Standard in vivo toxicity tests of the FCS and its constituents should be described in detail in the CTP. Both unpublished and published safety data should be included and presented in an organized fashion. Study reports and published articles of the same study type (i.e., subchronic, chronic, reproductive, etc.) should be grouped by species (e.g., mouse, rat, dog, etc.), then summarized in chronological order within each grouping. Following is one example of an outline that a notifier could follow to organize the studies within the CTP:

- Acute toxicity studies (may be presented in tabular form)
- Short-term toxicity studies
- Subchronic toxicity studies
  - Mouse
  - Rat
  - Dog
  - Other species
- Reproductive and developmental studies
- Chronic studies (by species).
- Carcinogenicity studies
- Special studies (including *in vitro* studies, as appropriate)

FDA recommends that each individual study summary include the following minimum information:

- Identity of test substance
- Animal species and strain(s) tested
- Number of animals/sex/dose and control groups
- Route of administration
- Doses (mg/kg bw/d), frequency and duration of dosing, and dosing vehicle(s), if any
- Other elements of study design, as appropriate (e.g., recovery phase, culling method, interim sacrifice, etc.)
- Parameters measured (e.g., clinical signs, clinical laboratory tests, organ weights, histopathology etc.) and the frequency of measurements
- Significant, compound-related effects (including doses at which effects were observed, incidences of animals with effects, etc.)
- Highest dose(s) at which no substance-related effect(s) were observed (*i.e.*, NOEL for each effect.)

B. Determination of No-Observed-Effect Level (NOEL)

A NOEL should be determined by the most sensitive, non-neoplastic adverse effect identified from relevant safety studies. The NOEL should be expressed in terms of mg per kg body weight per day of the test animal.

If the levels of the FCS or constituents given to test animals in a study are expressed as percent or parts per million in the diet, the notifier should report the NOEL using these units and also calculate intake on a mg per kg body weight per day basis. In these cases, the notifier should indicate if actual food consumption data were used in such calculations. A summary table of the adverse effects observed, if any, should be prepared by study type (*i.e.*, subchronic, chronic, reproductive, etc.) to facilitate the evaluation and determination of no-observed-effect levels for all of the substance-related effects.

C. Risk Assessment for Carcinogenic Constituents

The CTP should include risk assessments for carcinogenic constituents of FCSs, as appropriate. The Delaney clause of the Act's food additive provisions (sec. 409(c)(3)(A) of the Act) prohibits the approval of carcinogenic food additives including FCSs. Importantly, however, the Delaney clause applies to the additive itself and not to constituents of the additive. Therefore, if a food additive that is an FCS, has not been shown to cause cancer but contains a carcinogenic constituent, FDA evaluates the constituent under the general safety standard (sec. 409 (c)(3)(A) of the Act) using quantitative risk assessment procedures.

If the results of epidemiology studies or rodent carcinogenicity studies on the constituent are either positive or equivocal, the notifier ordinarily should calculate an extreme-case,

upper-bound, lifetime risk to humans from exposure to the constituent. A notifier may use another approach to estimate the risk presented by a carcinogenic constituent, and should present convincing scientific evidence to justify the alternative approach to estimate the risk. In calculating the risk, the notifier should:

1. use the tumor data from the most sensitive species, strain, sex, and study;

2. assume that tumors arising at multiple sites are independent of each other and add their risks; and

3. calculate the extreme-case, upper-bound, lifetime risk by multiplying the unit cancer risk by the estimated human exposure to the constituent based on its use level in the notification. The unit cancer risk is defined as the slope of a straight line drawn from the lowest apparent effect dose to zero. FDA has calculated the unit risk for some constituents of FCSs; these are available upon request.

General information on FDA's approach to risk assessment is contained in publications by Kokoski et al. (1990) and Lorentzen (1984). For more specific information on the Center for Food Safety and Applied Nutrition's quantitative risk assessment procedures, notifiers should contact FDA.

D. Bibliography

The CTP should include a bibliography with all references listed alphabetically. All published and unpublished studies and information presented in the CTP should be referenced appropriately in the text by citing the author(s) and year of publication. Each published reference should include the names of all authors, the year of publication, the full title of the article, pages cited, and name of publication. For a book, the reference also should include the title of the book, the edition, the editor(s), and the publisher. Reference to unpublished studies should identify all authors, the sponsor of the study, the laboratory conducting the study, the final report date, the full title of the final report, the report identification number, and inclusive page numbers. References to government publications should include the department, bureau or office, title, location of publisher, publisher, year, pages cited, publication series, and report number or monograph number.

VIII. FDA'S VIEWS OF THE RELEVANCE OF VARIOUS TYPES OF SAFETY STUDIES IN NOTIFICATIONS

With the exception of acute studies, FDA considers safety studies in which the test substance is given *via* the oral route most relevant to the safety assessment of substances in food. The data collected from studies using other routes of administration, including inhalation and dermal studies, may be of value if systemic effects at distal sites are observed. Only studies and information that are relevant to the safety assessment of a substance in food need be discussed in the CTP.

Below, FDA's views on the relevance of various types of toxicological studies to the safety assessment of an FCS are discussed in brief.

A. Acute Toxicity Studies

Acute toxicity data, including LD_{50} values, rarely are used in the overall safety assessment of FCSs to which long-term repeated exposure of consumers is expected. It is not necessary to discuss acute studies individually. An exception may be where there is significant and useful information that is provided by the acute toxicity study that may provide clues as to the potential target organs for the compounds adverse effect(s). Otherwise, the results of acute toxicity studies should be summarized in a table.

B. Genetic Toxicity Studies

FDA believes that information on the genetic toxicity of a substance is critical to the safety assessment of that substance because, in the absence of carcinogenicity data, genetic toxicity studies may be used to draw conclusions about its potential carcinogenicity.

Factors that should be considered in determining whether results of genetic toxicity studies indicate a potential safety concern for an FCS include:

1. Other available safety data such as bioassays;
2. The quality of the genetic toxicity studies;
3. The array of positive and negative genetic toxicity test results; and
4. The chemical structure of the substance (see IX).

C. Short-term Toxicity Studies

Short-term toxicity studies in animals, usually only 7-28 days in duration, should not be used to establish an ADI for an FCS. However, individual summaries of short-term studies should be included in the CTP. For these studies, endpoints or target organs potentially associated with toxicity and dose levels appropriate for longer-term toxicity tests should be emphasized, as appropriate.

D. Subchronic Toxicity Studies

NOELs from subchronic toxicity studies often are the basis for determining ADIs for FCSs. In such cases, it is important to provide complete summaries of subchronic studies, including detailed discussions of the study results in the CTP. If the primary objective of a subchronic study is to identify the target organ or select doses for a longer study, it may be appropriate to emphasize these objectives in the study summary. If subchronic studies are available in different species, species differences, if any, should be discussed.

E. Reproductive and Developmental Toxicity Studies

NOELs from reproductive and developmental toxicity studies may be the basis for determining ADIs for FCSs. Therefore, a summary and detailed discussion of the results of each study should be provided. For both parental animals and their offspring in each generation, no-effect levels should be identified for all substance-related changes. The summaries should state which effect(s) were used to derive NOELs. The toxicological relevance of any reported changes should be evaluated and, if observed, the impact of

concurrent maternal toxicity on the results of the study should be addressed.

F. Chronic Toxicity Studies

If chronic toxicity studies are available, the results of these studies will ordinarily supersede subchronic studies results for the purpose of assessing the safety of an FCS. Due to the longer duration of these studies, toxic effects may be identified that would not be detected in shorter- term studies. In the CTP, the results of chronic rodent or non-rodent studies should be summarized and discussed in detail.

G. Carcinogenicity Studies

Carcinogenicity studies are relevant to the safety assessment of FCSs and their constituents. When such studies are available, all neoplastic and non-neoplastic study observations should be discussed. Summary tables of treatment-related neoplastic and non-neoplastic lesions at any organ/tissue site should be prepared. The incidence of test animals with benign and malignant tumors at a specific organ site, both separately and combined, should be provided as appropriate (McConnell *et al.*, 1986; NTP Guidelines). If available, a detailed morphological description of any significant lesions should be included. Statistical trend tests should be performed in addition to tests of significance between dose and control groups. In addition, all effects observed should be evaluated for potential biological relevance. Related histopathological information, such as time to tumor formation and historical tumor data from performing laboratories, should be discussed. Reports prepared by the National Toxicology Program provide good examples of how the histopathological data requested above should be presented. The CTP should state clearly whether the FCS was associated with neoplastic or pre-neoplastic changes and discuss whether the incidence, location and type of tumors observed in this study demonstrate any carcinogenic effects attributable to the FCS or its constituents, as appropriate. Note that the detailed information described above is particularly important to support a conclusion that no carcinogenic effects were observed in a study.

H. Special Studies

Special studies include metabolism and pharmacokinetic studies, and other studies designed to test specific types of toxic effects in animals (*e.g.* neurotoxicity, immunotoxicity). Clinical studies, and observations reported in humans, are also considered special studies. Ordinarily, clinical studies are not a part of the testing paradigm for FCSs. However, if clinical studies are available, individual study summaries should be provided in the CTP. The results of clinical studies may affect the ADI determination for an FCS.

IX. EVALUATION OF STRUCTURAL SIMILARITY TO KNOWN TOXICANTS

It is reasonable to expect that the chemical structure and physicochemical properties of FCSs and their constituent(s) are potential determinants of toxicity. To the extent feasible, discussions or explanations that predict toxicity based on structure/activity relationships may be incorporated into the safety assessment of FCSs and their constituent(s). When appropriate, expert analysis, decision-tree procedures (*e.g.*, Cramer et al., 1978), or computer-assisted quantitative structure/activity techniques may be used to relate the chemical structure of a substance with a

toxicological endpoint of interest. Such information should not be considered as a substitute for actual data, but may be useful in developing an overall strategy for assessing the safety of a substance and interpreting the results of carcinogenicity and other types of safety studies.

X. PRE-SUBMISSION MEETINGS

A notifier may request a pre-submission meeting regarding a notification for an FCS. Many notifications will not require pre-submission interactions between FDA and the notifier. Such interactions will occur at the discretion of the notifier and are intended to facilitate the submission of successful notifications since notifications without adequate scientific support will not be accepted. FDA considers all pre-submission meetings consultative in nature. Pre-submission meetings should not be considered determinative with respect to FDA's decision to accept or object to a notification submitted to FDA subsequent to a pre-submission meeting.

One example of when a pre-submission meeting might be helpful is when the ADI/CEDI ratio is less than five. In such cases, the notifier may wish to request a meeting before submitting a notice to discuss possible interpretive differences in establishing a NOEL to calculate an ADI. Because dosing levels in safety studies are often spaced by a factor of three, the determination of the NOEL would seldom be expected to differ by more than a single dose. Therefore, FDA believes that when the ADI/CEDI ratio is less than five, a pre-submission meeting should be considered.

Pre-submission meetings may also be helpful when there are questions regarding the carcinogenicity of a FCS, significant risk potentially associated with a carcinogenic constituent, or when there are equivocal mutagenicity data.

XI. ADDITIONAL TOXICOLOGICAL CONSIDERATIONS IN DECIDING TO SUBMIT A NOTIFICATION

FDA's experience in evaluating the safety of FCSs and their constituents indicates that situations may arise in which a FCN will be appropriate for the use of an FCS even if the cumulative exposure for the FCS or its constituents is at or greater than 1 ppm, or 200 ppb in the case of biocides. Examples of such cases are provided below.

An FCN may be appropriate for an FCS, even if the estimated cumulative exposure is greater than 1 ppm, or 200 ppb for biocides, when:

There is an existing ADI for the FCS and its constituent(s). In such a case, the notifier should contact FDA to determine the applicability of the ADI for the FCS, before submitting an FCN.

A large database is available on a close structural analog of the FCS and its constituent(s), which analog has been approved by FDA. In such cases, the following toxicological tests are recommended to demonstrate the degree of toxicological and metabolic similarity between the FDA-regulated analog and the FCS and its constituent(s):

a. One 90-day oral toxicity study in a rodent or non-rodent species; and

b. Comparative absorption, distribution, metabolism, and elimination studies.

The FCS and/or its constituent(s) is poorly absorbed or is not absorbed from the gastrointestinal tract. Such assertions should be supported by relevant scientific information or data.

The FCS undergoes chemical or metabolic transformation solely to products known to be of little toxicological concern at the estimated level of CEDI. Such assertions should be supported by relevant *in vivo* or *in vitro* data.

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Content last updated by mac/msl on 2002-FEB-04
Hypertext last updated by mac/msl/emw 2002-MAR-01