

Preparation of Food Contact Substance Notifications (Toxicology Recommendations): Guidance for Industry

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Preparation of Food Contact Substance Notifications (Toxicology Recommendations): Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance at the phone number listed on the title page.

I. Introduction

Section 409 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) establishes a food contact substance 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 (section 409(h)(6) of the FD&C 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 our Threshold of Regulation Policy (21 CFR 170.39), or be the subject of a notification under section 409(h) of the FD&C Act that is effective (section 409(a)(3) of the FD&C 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 (sections 409(h)(1) and 409(b) of the FD&C Act). Section 409(b) of the FD&C 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.

¹ This guidance has been prepared by the Office of Food Additive Safety, Division of Food Contact Substances in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

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The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

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 Premarket Submissions 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). However, 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 FAP 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

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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 (GLP) regulations for non-clinical laboratory studies in 21 CFR 58.105 (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 Premarket Submissions 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 parts per billion \(ppb\) \(*i.e.*, 1.5 micrograms \(\$\mu\text{g}\$ /person/day\) 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 comprehensive toxicology profile (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 \(*i.e.*, 1.5 \$\mu\text{g}\$ /person/day\) but not exceeding 50 ppb \(*i.e.*, 150 \$\mu\text{g}\$ /person/day\)](#)
 - a. The potential carcinogenicity of an FCS (and/or a constituent, if appropriate) with a cumulative exposure between 0.5 ppb and 50 ppb

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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 thymidine kinase (tk[±]) gene mutation assay. FDA prefers the mouse lymphoma tk[±] gene mutation 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 \(*i.e.*, 150 µg/person/day\) 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[±] gene mutation 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[±] gene mutation 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 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.

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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 FAP be submitted for the FCS (see XI).

B. [Safety Testing Protocols](#)

FDA 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. (See [Guidance for Industry and Other Stakeholders: Toxicology Principles for the Safety Assessment of Food Ingredients](#) (Redbook 2000).)

The [Redbook 2000](#) sections available on FDA's internet site 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 us on proposed deviations from recommended safety test protocols before the tests are conducted.

All safety studies should be conducted according to FDA's GLP regulations, or the GLP guidelines of the EPA, or the guidelines of the OECD. If a study was not conducted in compliance with these 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 recommends 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.

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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 recommendations 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 information and recommendations discussed in this document permit 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 to determine 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 three sections: Section A- Safety Narrative, Section B- Comprehensive Toxicology Profile(s), and Section C- Relevant Toxicity Studies. 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](#)).

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Section 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 (NOELs). 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 in the SN.

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To calculate an ADI, the 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 Toxicology 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.

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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. The 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

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- Animal species and strain(s) tested
- Number of animals/sex/dose and control groups
- Route of administration
- Doses milligram/kilogram bodyweight/day (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/kg bw/d 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 NOELs 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 FD&C Act's food additive provisions prohibits the approval of carcinogenic food additives including FCSs (section 409(c)(3)(A)). 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 (section 409 (c)(3)(A) of the FD&C 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:

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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 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 median lethal dose (LD₅₀) 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

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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 to 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. The summary of these studies should discuss endpoints or target organs potentially associated with toxicity and dose levels that would be appropriate for longer-term toxicity studies.

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, NOELs 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.

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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; National Toxicology Program (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 NTP 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

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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. Prenotification Consultation (PNC) Meetings

A notifier may request a PNC meeting regarding a notification for an FCS. Many notifications will not require PNC 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 PNC meetings consultative in nature. PNC 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 PNC meeting.

One example of when a PNC 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 PNC meeting should be considered.

PNC meetings may also be helpful when there are questions regarding the carcinogenicity of an 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 an 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):

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- 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.

XII. Paperwork Reduction Act of 1995

This guidance contains information collections that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521).

The time required to complete this information collection is estimated to average 25 to 150 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Office of Food Additive Safety
Division of Food Contact Substances, HFS-275
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0495 (expires 03/31/2022).

XIII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500 and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the

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Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes, but websites are subject to change over time.

1. Cramer, G.M., Ford, R.A., and Hall, R.L. 1978. Estimation of toxic hazard - A decision tree approach. *Food Cosmet. Toxicol.* 16:255-276.
2. Kokoski, C.J., Henry, S.H., Lin, C.S., and Ekelman, K.B. Methods used in safety evaluation. In: *Food Additives*, edited by Branen, A.L., Davidson, P.M., and Salminen, S., Marcel Dekker, Inc., New York, p. 579-616, 1990.
3. Lorentzen, R. 1984. FDA Procedures for carcinogenic risk assessment. *Food Technology* 38(10):108-111.*
4. McConnel E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. 1986. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J. Natl. Canc. Inst.* 76:283-289.

Document History

- April 2002 – First edition of guidance was issued.
- October 2021 – The guidance was updated to include Paperwork Reduction Act information and non-substantive formatting or editorial revisions.