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Preparation of Food Contact Notifications for Food Contact Substances in Contact with Infant Formula¹ and/or Human Milk: Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1200.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition**

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¹ Under 21 CFR 106.3, *infant formula* means a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.

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Preparation of Food Contact Notifications for Food Contact Substances in Contact with Infant Formula and/or Human Milk: Guidance for Industry²

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration's (FDA or we) on this topic.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 as listed on the title page.

I. Introduction

We are providing this guidance to represent our current thinking on recommendations for preparation of food contact notification (FCN) submissions for food contact substances (FCSs)³ used in contact with infant formula and/or human (breast) milk.

This document is intended to provide specific guidance to help manufacturers or suppliers submitting an FCN in the safety assessment of FCNs for substances that are intended for use in contact with infant formula and/or human milk. FCSs that would be affected by this guidance document may include infant formula packaging for both liquid (concentrate and ready to feed) and powdered formula, baby bottles, bottle inserts, nipples, and any other materials that are in contact with infant food.⁴

² This guidance has been prepared by Office of Food Additive Safety, Division of Food Contact Notifications in the Center for Food Safety and Applied Nutrition at the Food and Drug Administration.

³ 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 FD&C Act) (21 U.S.C. 348) to establish an FCN process as the primary method by which FDA regulates food additives that are 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 such use of the substance is not intended to have any technical effect in such food.

⁴ For purposes of this guidance our use of the phrase "infant food" is limited to infant formula and human milk.

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There has been increased scientific interest in the role of human lifestages in the evaluation of chemical safety (Makris *et al.*, 2008). This interest has largely been spurred by scientific advances in the fields of developmental biology and toxicology that suggest that different lifestages, particularly pediatric lifestages, involve fundamental biological differences that may influence responses to chemical exposures (Bruckner, 2000; Scheuplein *et al.*, 2002; Ginsberg *et al.*, 2004a,b; Felter *et al.*, 2015). These scientific advances have caused us to reevaluate our approach to the safety assessment of FCSs that contact infant food. Not only does exposure to such FCSs occur during a period of important developmental processes (Neal-Kluever *et al.*, 2014), but infants also frequently consume infant formula and/or human milk exclusively for the first 6 months of life.⁵ Because infants consume greater amounts of food relative to their body weight than do adults (Lawrie, 1998),⁶ this developmental period is the period of highest intake of food contact migrants relative to body weight (Neal-Kluever *et al.*, 2014).

This guidance describes our thinking as to how manufacturers or suppliers of FCSs intended for infant food use should consider these dynamics. Notifications for FCSs must contain sufficient scientific information to demonstrate that the substance that is the subject of the notification is safe for the intended use (section 409(h) of the FD&C Act). This guidance contains recommendations regarding how the scientific information in FCNs for infant food uses should demonstrate that the FCS is safe for the specific intended use.

While the period of infancy extends beyond the first 6 months after birth, we recognize that the period during which infants exclusively consume human milk and/or infant formula may largely be restricted to the first 6 months.⁷ Therefore, this guidance focuses only on the 0-6 month age range. For the purpose of this guidance document, the term “infant” refers to individuals aged 0-6 months.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

FDA has previously provided guidance for the safety assessment of FCSs.⁸ Our previous guidance, however, does not specifically address dietary exposure and safety assessment

⁵ The American Academy of Pediatrics recommends consumption of only formula and/or human milk to the age of 6 months (<http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Age-Specific-Content/Pages/Infant-Food-and-Feeding.aspx#none>).

⁶ See National Health and Nutrition Examination Survey (NHANES) data at <http://www.cdc.gov/nchs/nhanes.htm>.

⁷ See recommendation of the American Academy of Pediatrics, *available at* <http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Age-Specific-Content/Pages/Infant-Food-and-Feeding.aspx#none>.

⁸ See U.S. Food and Drug Administration, Guidance for Industry: Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations, Final Guidance, Revised April 2002,

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considerations related to the migration of chemical substances from packaging and other food contact articles as it pertains to infants. This guidance helps fill this gap, and is based on the scientific advances described in section I of this guidance. Consumer exposure to any one food chemical is expected to be relatively low in adults and children, as adults and children eat a variety of foods packaged in a variety of materials. However, infants aged 0-6 months typically consume human milk and/or infant formula exclusively and consume higher amounts of food in relation to their body weight than an adult. These factors contribute to a higher, albeit temporally limited, exposure to potential migrants from the FCSs.

There are clear differences between adults and infants when comparing pharmacokinetic parameters (e.g., metabolism). Differences in metabolic capacity result in different metabolic profiles between adults and infants (Alcorn and McNamara, 2003; Ginsberg *et al.*, 2004a,b; Ginsberg *et al.*, 2002). The metabolic profile of infants can result in either increased or decreased susceptibility to the toxicity of chemicals, depending on, for example, whether metabolism results in biological activation or inactivation of the chemical (U.S. EPA 2002b, 2005a; Ginsberg *et al.*, 2004a,b; Ginsberg *et al.*, 2002). Compared to adults, other factors that can influence the biological responses of infants to chemicals include body water to lipid ratios, altered levels of plasma proteins, altered organ perfusion rates, maturation of cellular transporters, and differences in water and food intake (relative to body weight) (Alcorn and McNamara, 2003; Ginsberg *et al.*, 2004a,b; Landrigan and Goldman, 2011).

In addition to differences in pharmacokinetic processes, infants undergo distinctive periods of rapid growth and development. The rapid growth, extensive tissue reorganization, and cellular changes associated with structural maturation and functional differentiation during the developmental period of 0-6 months may result in enhanced susceptibility to toxicants that may initiate chronic disease. The brain, reproductive organs, endocrine system, immune system, kidney, liver, and skeleton in infants are immature at birth and may be susceptible to toxic insult during maturational processes (Zoetis *et al.*, 2003; Zoetis and Hurtt, 2003; Watson *et al.*, 2006; Cappon *et al.*, 2009; Schwenk *et al.*, 2003). For example, neurodevelopmental effects from exposure to chemicals, such as lead, methyl mercury, and some pesticides, during brain development are well established (Grandjean and Landrigan, 2006). Links between early life exposure to certain chemicals and other outcomes, such as developmental immunotoxicity and inflammatory diseases (e.g., atherosclerosis, coronary heart disease), also have been suggested (DeWitt *et al.*, 2012a; Leifer and Dietert, 2011).

The importance of this developmental period and the potential for elevated exposures on a body weight basis suggests that these parameters be considered when assessing the safety of components of FCSs in contact with infant food. FCN submissions for substances that will contact human milk and/or infant formula should therefore consider the myriad of biological changes and growth during the developmental period and whether infants are more or less sensitive than the general population when exposed to equivalent levels of migrants from FCSs.

(<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081825.htm>), referred to in this guidance as the “[2002 toxicology guidance](#)”.

III. Recommendations

A. Chemistry Recommendations

1. Migration Testing

Our general recommendations pertaining to chemistry information that should be submitted in a FCN are outlined in our [2007 chemistry guidance](#) for FCSs.⁹ As described in our [2007 chemistry guidance](#), the concentration of an FCS in the daily diet may be determined from measured levels in food or in food simulants. It may also be 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 we always accept reliable analyses of FCSs in real foods, in practice, many analytes are difficult to measure in real foods. As an alternative, manufacturers or suppliers may submit migration data obtained with food simulants that reproduce the nature and amount of migration of the FCS into food. The submitted migration data should reflect the most severe temperature/time conditions to which the food-contact article containing the FCS will be exposed. The recommendations outlined below are specific to those FCSs intended for use in infant food contact applications.

a. Food Simulant

Test protocols (including those in our [2007 chemistry guidance](#)) recommend the use of 10% ethanol as a food simulant for aqueous and acidic foods (i.e., Food Types I, II, IV-B, VI-B, and VII-B, including milk products identified as oil-in-water emulsions (Food Type IV-B)).¹⁰ Recently, studies conducted in conjunction with the “[Food Migrosure](#)” [migration modeling project](#) suggest that 50% ethanol might be a more appropriate general simulant for liquid dairy products because it more closely tracks the actual migration levels of many dairy products.¹¹ As such, we consider 50% ethanol as a generally appropriate simulant for infant formula (liquid or otherwise reconstituted) and human milk. We also consider 50% ethanol as a generally accepted simulant for non-dairy based infant formulas, such as soy-based infant formulas, since the fat content of such formulas is similar to the fat content of milk-based infant formulas. This simulant will cover the range of formula compositions and account for the varying fat content of individual products. The use of 95% ethanol also has been found to be an effective fatty-food

⁹ U.S. Food and Drug Administration, Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations, Revised December 2007, (<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081818.htm>), referred to in this guidance as the “[2007 chemistry guidance](#)”.

¹⁰ For further information on food types, see Appendix V of [2007 chemistry guidance](#) or <http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/FoodTypesConditionsofUse/default.htm>.

¹¹ The aim of the “[Food Migrosure](#)” [project](#) was to extend existing migration models that are currently applied to food simulants to food itself. The foods applicable to this guidance include condensed milk (10% fat) and whipping cream (30% fat), representing fatty foods, and milk powder, representing dry foods (www.foodmigrosure.org). Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. *Official Journal of the European Union*, Volume L12, pp. 1-89.

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simulant; however, it may exaggerate migration. We provide our current thinking for simulants for powdered infant formula immediately following in section III.A.1.b.i of this guidance.

b. Migration Protocols

i. Articles in Contact with Packaged Formula

Liquid formula (both concentrate and ready-to-feed) lawfully marketed in the United States is primarily packaged in plastic containers or polymer-coated metal cans and is frequently intended to be thermally treated by the manufacturer in the container. Our recommended migration testing protocols for this type of thermal treatment are the same as those described for single use articles in Appendix II, section 1, “General Protocols (Single-Use Applications) Corresponding to Condition of Use” of our [2007 chemistry guidance](#), and are intended to model thermal treatment and extended storage conditions. For polymer-coated metal cans, where the contents are retorted in the can, Condition of Use A is recommended. As provided in our [2007 chemistry guidance](#), Condition of Use A includes the food contact article being heat-sterilized or retorted under transient temperatures (ca. 121 °C (250 °F)). For plastic articles where sterilization occurs outside the container, other conditions of use may be appropriate. As discussed in our [2007 chemistry guidance](#), a food mass-to-surface area ratio of 10 grams per square inch (10 g/in²) should be used to convert migration values to a concentration in infant food.

Powdered formula lawfully marketed in the United States is primarily packaged in paper-aluminum foil composite cans or plastic tubs and is not intended to be thermally processed or retorted in the container. To determine migration into powdered formula, we recommend that testing be conducted with 50% ethanol, or a dry food simulant such as Tenax (Poly(2,6-diphenylphenylene oxide)), or other appropriate medium. The use of a liquid food simulant for powdered formula would result in a worst-case migration estimate. Our recommended migration testing protocol for this application is the same as that recommended under Condition of Use E (*Room temperature filled and stored (no thermal treatment in the container)*) in Appendix II, section 1 of our [2007 chemistry guidance](#). That is, we recommend that the manufacturer or supplier conduct migration studies for 240 hours at 40 °C (104 °F). We also recommend that the test solutions be analyzed after 24, 48, 120, and 240 hours, and that any calculations use a food mass-to-surface area ratio of 10 g/in² and account for the powder concentration in reconstituted formula (on average about 13%).

ii. Articles in Contact with Infant Food for Feeding (e.g., baby bottles)

Baby bottles are generally intended for repeated use by infants and are typically made of glass or polymers, such as polypropylene.

When human milk and infant formula are consumed through baby bottles, some thermal treatment of the human milk or formula in the bottle may occur (e.g., from conditions as mild as warming of formula before feeding to simultaneous sterilization of water and bottles). We recommend testing according to either Condition of Use B (*Boiling water sterilized*) in Appendix II, section 1 of our [2007 chemistry guidance](#), or Appendix II, section 4 (Articles Intended for Repeated Use). As set forth in our [2007 chemistry guidance](#), Condition of Use B involves the

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same protocol as for Condition of Use A, except that the highest test temperature in Condition of Use B is 100 °C (212 °F). Including this highest test temperature should adequately represent the time-temperature-use conditions encountered in the preparation, holding, storage, and/or feeding of infant food in articles such as nursing bottles. An alternative approach for conducting migration studies that we also recommend is following the recommendations in Appendix II, section 4, of our [2007 chemistry guidance](#). As set forth in section 4 of our [2007 chemistry guidance](#), migration studies may be conducted with 50% ethanol for 240 hours at the highest intended temperature of use.

As further discussed in Appendix II, section 4, of our [2007 chemistry guidance](#), estimates of the weight of food contacting a known surface area over the service lifetime of the repeat-use articles are also used to estimate exposure. Together with the migration data, this will allow calculation of migration to all the food processed over the service life of the article. We recommend that the estimate for the mass of food contacting a known surface area should take into account the fact that baby bottles may be used multiple times a day and over a period of several months. Based on these factors, we have determined that a food mass-to-surface area ratio of 1400 g/in² is adequate to represent the mass of food that would contact a feeding bottle over its service lifetime. We recommend that the food mass-to-surface area ratio of 1400 g/in² be used to convert migration values to a concentration in infant food for this repeat use scenario.

iii. Other Articles

For notifications involving other food contact articles intended to contact human milk and/or infant formula, we recommend that manufacturers or suppliers consult with us through a Premarket Notification Consultation (PNC) before submitting an FCN. (See section III.C.5 of this guidance for further information on the PNC process.)

iv. Alternatives to Testing on Food Contact Articles

In the absence of validated migration studies, migration levels to food may also be assessed by the assumption of 100% migration of the FCS to food. Alternatively, migration modeling could also be used if the applicable parameters are known. For further guidance regarding migration modeling, consult our [2007 chemistry guidance](#).

2. Exposure Estimation

As discussed in section II.E of our [2007 chemistry guidance](#), exposure estimates for FCSs are generally based on “Consumption Factors” and “Food-Type Distribution Factors.” These factors are average values for all foods expected to contact specific types of packaging materials. They are not based on consumption patterns typical of the infant period because infants aged 0-6 months frequently consume human milk and/or infant formula exclusively and infants often rely on one or just a few brands of infant formula or baby bottles. Accordingly, we do not recommend use of Consumption Factors or Food-Type Distribution Factors for calculating exposure to infant food.

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The exposure of certain sub-populations of interest to an FCS can be estimated by examining foods specific to the population group of interest, and then assessing the food-contact articles that may contain the FCS. This is frequently done using information on the consumption of a specific food(s) derived from food consumption survey data. We recommend considering the intakes of the identified foods and the concentration of the substance in each of those foods.¹²

To apply this approach to FCSs that are intended to contact infant food, we have developed default values for both infant body weight (6.3 kg-bw/infant) and infant food consumption (900 g formula/infant/day) that were determined based on the 2-day 2005-2010 National Health and Nutrition Examination Survey (NHANES) food consumption survey. These values resulted in a consumption-to-mass ratio of 140 grams per kilogram body weight per day (140 g/kg bw/d), or 0.14 kg/kg bw/d. We recommend calculating the estimated daily intake (EDI) of the FCS for infants by multiplying the migration of the substance to infant food (in parts per billion (ppb) or micrograms per kilogram ($\mu\text{g}/\text{kg}$)) by 0.14 kg/kg bw/d. As an example, if the concentration of the FCS in food is 1 $\mu\text{g}/\text{kg}$, then the calculation would be:

$$\begin{aligned}\text{EDI} &= (1 \mu\text{g FCS}/\text{kg formula})(0.14 \text{ kg formula}/\text{kg-bw}/\text{d}) \\ &= 0.14 \mu\text{g FCS}/\text{kg-bw}/\text{d}\end{aligned}$$

B. Toxicology Recommendations

The toxicology recommendations in this section provide a flexible approach for addressing specific endpoints that may be relevant to a manufacturer's or supplier's determination that the intended use of the FCS in contact with infant formula and/or human milk is safe. In general, we recommend that manufacturers or suppliers develop their safety assessment based on the estimation of exposure, and that other available scientific information on the FCS also inform the manufacturer or supplier as to the type of testing and safety analysis needed to demonstrate that the FCS is safe for the intended use under section 409(h) of the FD&C Act. As described in section III.B.2 of this guidance, it may be appropriate to conduct additional safety testing, beyond the safety testing recommended in our [2002 toxicology guidance](#) to assess the safety of an FCS for infants 0-6 months of age.

1. Exposure Based Testing Tiers

Our [2002 toxicology guidance](#) makes testing recommendations based on four tiers. For each tier, we make recommendations for studies and other information to assess the safety of an FCS (and each constituent as appropriate). Each tier in our [2002 toxicology guidance](#) is based on exposure calculated in micrograms per person per day ($\mu\text{g}/\text{p}/\text{d}$), and includes the assumption of 60 kg of body weight per person as well as consumption amounts that are not specific to the infant period.¹³ To account for differences between general and infant populations with respect to body

¹² See discussion of sub-populations in [U.S. Food and Drug Administration, Guidance for Industry: Estimating Dietary Intake of Substances in Food](#), August 2006. (<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm074725.htm>)

¹³ The four tiers in the [2002 toxicology guidance](#), expressed in $\mu\text{g}/\text{p}/\text{d}$ are: (1) Incremental exposure at or less than 1.5 $\mu\text{g}/\text{p}/\text{d}$; (2) cumulative exposure greater than 1.5 $\mu\text{g}/\text{p}/\text{d}$ but not exceeding 150 $\mu\text{g}/\text{p}/\text{d}$; (3) cumulative exposure

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weight and food intake, we have normalized the exposure values for each of the four tiers in our [2002 toxicology guidance](#). The normalized tiers, which are set forth in Table 1, are based on estimated daily intakes expressed as micrograms per kilograms of body weight per day ($\mu\text{g}/\text{kg}$ bw/d). To determine the recommended tier for the infant food contact toxicological evaluation, manufacturers or suppliers should calculate the estimated daily intake for infants considering the intended use of the substance that is the subject of the notification. The estimated daily intake should also include any other uses specifically authorized for infant food-contact use. The method for calculating the estimated daily intake should be applied to the FCS and each constituent as appropriate. Manufacturers or suppliers should then use the estimated daily intake values to determine the applicable tier, using Table 1.

Table 1: Tier Values:

Tier Level	Exposure Value (from 2002 toxicology guidance)	Normalized Exposure Value ($\mu\text{g}/\text{kg}$ bw/d)
Tier 1	$\leq 1.5 \mu\text{g}/\text{p}/\text{d}$	$\leq 0.025 \mu\text{g}/\text{kg}$ bw/d
Tier 2	$>1.5 \mu\text{g}/\text{p}/\text{d}$ to $< 150 \mu\text{g}/\text{p}/\text{d}$	>0.025 to $< 2.5 \mu\text{g}/\text{kg}$ bw/d
Tier 3	$\geq 150 \mu\text{g}/\text{p}/\text{d}$ to $< 3000 \mu\text{g}/\text{p}/\text{d}$	≥ 2.5 to $< 50 \mu\text{g}/\text{kg}$ bw/d
Tier 4	$\geq 3000 \mu\text{g}/\text{p}/\text{d}$	$\geq 50 \mu\text{g}/\text{kg}$ bw/d

2. Minimum Testing Recommendations

We recommend that FCNs for substances intended for use in contact with infant food refer to our [2002 toxicology guidance](#) for testing recommendations based on tier level.¹⁴ That is, for FCSs that fall within Tier 1, we recommend that FCNs follow the corresponding recommendations for safety testing in section IV.A.1 in our [2002 toxicology guidance](#). For FCSs that fall within Tier 2, we recommend that FCNs follow the corresponding recommendations for safety testing in section IV.A.2 in that guidance. For FCSs that fall within Tiers 3 and 4, we recommend that FCNs follow the corresponding recommendations for safety testing in sections IV.A.3 and IV.A.4 in that guidance, respectively. As with the recommendations in our [2002 toxicology guidance](#), the recommendations in this guidance are consistent with the general principle that the potential risk of a substance is likely to increase as exposure increases.

Although the tiered recommendations provide our general thinking regarding the type of testing and information that may be appropriate for assessing safety, there may be circumstances where we would recommend additional information and/or data in order to determine the safety of an FCS for use in contact with infant formula and/or human milk. Such circumstances are likely to arise if there is inadequate information to assess safety for use in contact with infant formula and/or human milk, or where there is information suggesting potential toxicity or other safety concerns. As noted in section II. Background of this guidance, the infant developmental period is characterized by continuous changes in physiological processes, such as pharmacokinetic parameters and organ and system development, which suggests that the minimum testing

between $150 \mu\text{g}/\text{p}/\text{d}$ and $3 \text{ mg}/\text{p}/\text{d}$; and (4) cumulative exposure at or greater than $3 \text{ mg}/\text{p}/\text{d}$. See section IV.A. of the [2002 toxicology guidance](#).

¹⁴ See section IV.A of the [2002 toxicology guidance](#).

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recommendations for the four tiers identified in our [2002 toxicology guidance](#) may not always be adequate to assess the safety of an FCS that contacts human milk and/or infant formula consumed during this period of early development (Neal-Kluever *et al.*, 2014).

Additional testing or safety information beyond the recommendations for each of the four tiers in our [2002 toxicology guidance](#) may be necessary to determine whether an FCS is safe for its intended use in contact with human milk and/or infant formula. Manufacturers or suppliers should consider, among other things, the potential for a toxic response in the apical endpoints with known developmental differences. Such potential may be identified as a result of available toxicity data, chemical structure(s), structure activity methods, or other resources,¹⁵ and may indicate a potential for developmental toxicity (such as neurotoxicity, immunotoxicity, reproductive toxicity, or other endpoints).¹⁶ Additionally, effects may be identified in juvenile or adult animal toxicity studies that may predict a different effect or change in magnitude or sensitivity in an infant. Information on absorption, distribution, metabolism, and excretion (ADME), mode of action (MOA), toxicokinetic (TK), toxicodynamic (TD), and/or pharmacokinetic (PK) profile may be useful in evaluating safety.

When designing studies and evaluating data to reduce uncertainty in the safety assessment for infant exposures, we recommend considering that PK, ADME, TK/TD, and/or other relevant data can be incorporated to more accurately describe interspecies differences or differences between juvenile and adult animals. We also recommend considering that the type of study and any specialized endpoints or modifications added to reproductive/developmental studies may be informed by the results of subchronic studies and additional available information. In addition, manufacturers or suppliers should understand any gaps relevant to infant exposure in the safety studies on which they rely and identify ways to address them. For example, a subchronic study, as described in our [2002 toxicology guidance](#), does not include dosing during the postnatal development period. Additionally, the protocols for most reproductive/developmental toxicity studies do not include estimation of exposure of a substance from human milk. Moreover, they typically do not include direct dosing of neonatal or juvenile animals during the postnatal period. These potential gaps in study design might be addressed by modifying subchronic or other studies (for example, see Delclos *et al.*, 2014), by use of PK/ADME data, and/or by use of other information related to the structure of the chemical to determine if exposure would be expected through lactation and whether the expected exposure can be quantified. Given the variety of different potential study design gaps and areas of uncertainty, manufacturers or suppliers should, as a general matter, consider whether it is necessary to modify traditional toxicity studies to

¹⁵ Examples of possible resources include: Structure-activity relationship (SAR; e.g., EFSA, 2011), Cramer classes (Cramer *et al.*, 1978), or the National Center for Toxicological Research Endocrine Disruptor Knowledgebase (EDKB) <http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm>. These are examples only and not an exhaustive list.

¹⁶ This information may be identified during preparation of the comprehensive toxicological profile (CTP), which, as described in the [2002 toxicology guidance](#), serves to identify all unpublished and published safety studies and related information relevant to the safety assessment of the FCS and to address all safety studies that identify adverse effects of the substance.

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account for the unique features of the early developmental period, as certain traditionally-used studies may not be suitable.¹⁷

The following are examples of scenarios in which additional or modified studies may be recommended to demonstrate the safety of FCSs for infant food uses. These examples are not inclusive or representative of all scenarios of when additional studies or study modifications may be recommended to demonstrate safety. For our examples, we assumed that the estimated exposure to a chemical ranges from 2.5 to ≤ 50 $\mu\text{g}/\text{kg}$ bw/d (Tier 3), such that, at minimum, the standard data package for Tier 3 as outlined in section IV.A.3 of our [2002 toxicology guidance](#) would ordinarily be recommended. The examples describe how relevant information could be considered in the interpretation of the standard data package (in this case Tier 3) and whether possible modifications or additions to the standard data package may be warranted.

- Alerting information (hazard identification) for toxicity relevant to the infant developmental time period (e.g., renal toxicity) was observed in an *in vivo* study in adult or juvenile animals. For example, a modified 90-day subchronic toxicity study initiated in the early postnatal time period in rodents (Postnatal Day 1-5) with direct dosing of neonatal and juvenile rodents (pups) may address the safety concern in this scenario.
- Alerting information (hazard identification) relevant to ongoing, long term, or latent effects (e.g., reproductive, endocrine, or neurological effects; or immunotoxicity) was observed in an *in vivo* study in adult or juvenile animals. In the absence of other safety information, a study (e.g., a two-generation or extended one-generation assay with possible modifications such as direct dosing of pups) may address the safety concern in this scenario.

Conversely, there may be situations in which we would not recommend additional studies. For example:

- Available information or studies indicate that there is no elevated risk or differential susceptibility for toxicity in pre-weaned animals. A 90-day study in juvenile/adult animals may be sufficient to support the safety of a chemical in this scenario, and no additional studies would be needed.

3. Age Dependent Cancer Risk Analysis of Carcinogenic Constituents

An FCN should include risk assessments for carcinogenic constituents of FCSs, as appropriate.¹⁸ If the results of epidemiology studies or rodent carcinogenicity studies on the constituent are

¹⁷ To the extent that manufacturers or suppliers may seek additional information about the possible considerations in study design specific to the early postnatal period, we note that several recent studies have addressed this issue. Examples include: Neal-Kluever *et al.*, 2014; Delclos *et al.*, 2014; Churchwell *et al.*, 2014; Moser *et al.*, 2005; and note 17 in ICH S5(R2), (2005). For specific information about FDA's recommendations for study design in a particular scenario, manufacturers or suppliers should contact FDA.

¹⁸ Section 409(c)(3)(A) of the FD&C Act prohibits the approval of food additives, including FCSs, found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the

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either positive or equivocal, the manufacturer or supplier ordinarily should calculate an extreme-case, upper-bound, lifetime risk to humans from exposure to the constituent. A manufacturer or supplier may use another approach to estimate the risk presented by a carcinogenic constituent and should present scientific evidence justifying their alternative approach. Our [2002 toxicology guidance](#) contains guidance for calculating the lifetime risk, but does not contain guidance regarding the role of infant exposure in contributing to the lifetime risk. However, the U.S. Environmental Protection Agency (EPA) has published guidance for assessing cancer risk from early-life exposure (U.S. EPA 2005a, 2005b, 2011), and it is our view that the EPA guidance provides a helpful framework for evaluating lifetime cancer risk (LCR) from infant exposure to FCSs that contact infant formula and/or human milk. EPA's guidance addresses the 0-2 year age range based on exposure. We have modified EPA's cancer risk equations to include the specific 0-6 month exposure scenario in the 0-2 year age as set forth below. We recommend that manufacturers or suppliers apply the equations below if the results of epidemiology studies or rodent carcinogenicity studies on the constituent are either positive or equivocal in order to assess LCR. A manufacturer or supplier may use another approach to estimate the LCR presented by a carcinogenic constituent, and should present scientific evidence justifying their alternative approach. The equations that we recommend for assessing LCR are as follows:

Risk for birth through 6 months:

$$R_{0-6 \text{ mos}} = \text{Unit Cancer Risk (UCR)} \times 10 \times \text{infant exposure} \times (0.5\text{yr}/78\text{yr})$$

Risk for 6 months through 2 years:

$$R_{6 \text{ mos}-2 \text{ yrs}} = \text{UCR} \times 10 \times \text{general population exposure} \times (1.5\text{yr}/78\text{yr})$$

Risk for 2 years to 78 years:

$$R_{2-78 \text{ yrs}} = \text{UCR} \times \text{general population exposure} \times (76\text{yr}/78\text{yr})$$

$$\text{LCR} = R_{0-6 \text{ mos}} + R_{6 \text{ mos}-2 \text{ yrs}} + R_{2-78 \text{ yrs}}$$

As the equations make clear, we recommend that manufacturers or suppliers calculate the extreme-case, upper-bound, lifetime risk by first conducting three separate calculations that involve: (1) the unit cancer risk or UCR; (2) the estimated exposure for each specific population exposure; (3) the age-dependent adjustment factor (ADAF) based on age; and (4) percent of lifespan for each age group. The three different calculations represent risk from exposure during the 0-6 month age period; risk from exposure during the 6 month through 2-year age period; and risk from exposure during the 2-year through 78-year age period. LCR represents the sum of the risk from all three age periods. The average lifespan age of 78 years is used in the equations and reflects the current average U.S. lifespan (Kochanek *et al.*, 2011).

As described above, these equations for assessing LCR includes an age-dependent adjustment factor (ADAF). As a general matter, we recommend an ADAF of 10 to account for the potential variability (increased susceptibility) during the developmental periods of 0-6 months and 6 months-2 years. This ADAF was recommended in certain scenarios in EPA's 2005 supplemental guidance (U.S. EPA 2005b) to incorporate early life susceptibility into cancer risk

safety of food additives, to induce cancer in man or animal. Importantly, section 409(c)(3)(A) applies to the additive itself and not to constituents of the additive. If a food additive that is an FCS has not been shown to cause cancer in man or animal, but contains a carcinogenic constituent, FDA will evaluate the safety of the constituent under the general safety standard (section 409(c)(3)(A) of the FD&C Act) using quantitative risk assessment procedures.

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assessment, and it reflects the possibility that different age groups may be less or more responsive to effects of carcinogens from FCSs. However, a manufacturer or supplier may use another ADAF or no ADAF to estimate LCR if it is scientifically justified. Such scientific evidence may exist if, for example, TK/TD or MOA data suggest lesser or greater susceptibility in the infant population.

Although we generally recommend the use of the above equations for assessing LCR, there may be circumstances when modification of the formula is appropriate. We suggest manufacturers or suppliers consult us if they believe such circumstances exist.

C. Administrative Recommendations

1. Acknowledgement of an FCN

We intend to continue acknowledging receipt of an FCN in writing within 30 days of receipt. This acknowledgment informs the manufacturer or supplier of the date when we received the complete FCN, and thereby the effective date of the notification if we do not object to the marketing of the substance. The acknowledgment also identifies the substance and use that is the subject of the notification.

In cases where the FCN does not designate an infant FCS use, the acknowledgment letter will include language in the “Limitation/Specifications” section indicating that, because the use of the FCS does not explicitly include a use for contact with infant formula and/or human milk, we are restricting our review to exclude these uses and are instead including in our review the general exposure from other food contact uses.

For further information on “Intended Use” and “Limitations/Specifications” language, *see* <http://www.accessdata.fda.gov/scripts/fdcc/?set=fcn>.

On the other hand, if the FCN specifies infant food use, we recommend that the manufacturer or supplier demonstrate the safety of the infant food use in accordance with this guidance. In such cases, the acknowledgement letter will state that the intended use of the FCS includes uses for contact with human milk and/or infant formula, as specified in the notification. Specifically, the “Intended Use” and “Limitations/Specifications” sections of acknowledgement letters will indicate that the intended use includes contact with infant food.

Manufacturers or suppliers should review carefully the description of the intended conditions of use and applicable limitations/specifications in the acknowledgment letter, as this will determine the uses for which the notification will become effective within the meaning of section 409(h) of the FD&C Act (21 U.S.C. 348(h)). The description also will affect the language that we include in the “Intended Use” and “Limitations/Specifications” sections in our Inventory of Effective Notifications (see section III.C.4 of this guidance for more information about our Inventory).

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2. Nonacceptance of an FCN

If any element of a notification required under 21 CFR 170.101(a) through (e) is missing, we will not accept the FCN for review, and we will provide the manufacturer or supplier with a nonacceptance letter (see 21 CFR 170.104(b)(1)). Under § 170.101(a) and (b), an FCN submission must include a comprehensive discussion of the basis for the manufacturer's or supplier's determination that the use of the FCS is safe. As provided in § 170.101(a)(1) and (2), this discussion must discuss all information and data submitted in the notification and address any information and data that may appear to be inconsistent with the determination that the proposed use of the FCS is safe. In addition, under § 170.101(b) all data and other information that form the basis of the determination that the FCS is safe under the intended conditions of use must be included. In evaluating what constitutes a comprehensive discussion of the basis of the manufacturer's or supplier's determination that the use of the FCS is safe, we consider each FCN on a case-by-case basis. Depending on the intended use of an FCS for use in contact with infant formula and human milk and the nature and extent of the safety discussion provided, we may determine that, in order for the discussion to be comprehensive, the discussion needs to include data and information relevant to infant exposure and safety. In such cases, we may determine on a case-by-case basis that the failure to provide such data and information causes the FCN to be incomplete and therefore subject to nonacceptance under § 170.104(b)(1). In most cases, we will provide the manufacturer or supplier an opportunity to supply the missing information, modify the use, or withdraw the FCN.¹⁹ If a manufacturer or supplier initially submits an FCN for an FCS that is not intended for use in contact with human milk and/or infant formula, but then later wishes to expand the uses for which the notification is effective to include such infant food contact uses, we may recommend submission of a new FCN. In such circumstances, we will recommend that the manufacturer or supplier consult this guidance and consult with us during the Premarket Notification Consultation (PNC) process. *See* section III.C.5 of this guidance for further discussion of the PNC process.

3. Final Letter

We are not required to issue a letter in response to the FCN if we do not object to the marketing of the notified substance. However, we realize that such a letter may serve to bring the review process to closure. Therefore, our policy is to issue a letter to the manufacturer or supplier that includes information identifying the FCS that is the subject of the notification and the date on which the notification became effective. The letter will include any applicable statements regarding infant food contact use in the "Limitations/Specification" section. (See section III.C.1. Administrative Recommendations --- Acknowledgment of an FCN.)

4. Inventory of Effective FCNs

We maintain an inventory of effective FCNs on our internet site. This inventory is the primary vehicle for informing the public of effective FCNs. The inventory contains information on the

¹⁹ In accordance with 21 CFR 170.103, a manufacturer or supplier may withdraw an FCN for an FCS, without prejudice to a future submission, at any time prior to the completion of FDA's review.

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identity of the substance that is the subject of the notification, the conditions of use shown to be safe, any limitations on the use of the substance, specifications for the substance, the manufacturer or supplier for whom the notification is effective, the date on which the notification became effective, and a tracking number. The inventory is publicly available on our internet site at <http://www.accessdata.fda.gov/scripts/fdcc/?set=fcn>. For FCNs with explicit authorization for use in contact with infant formula and/or human milk, we will indicate such use(s) in the “Intended Use” section of the web listing in the FDA inventory. For those FCNs whose FCS is not intended for use in contact with infant formula and/or human milk, the inventory will make clear that the FCSs are not intended for such use.

5. Premarket Notification Consultations (PNCs)

We recommend that manufacturers or suppliers use the PNC process to seek guidance on determining infant exposure and/or appropriate testing methods for infant FCSs. A manufacturer or supplier may request a pre-submission meeting/consultation with us regarding a notification for an FCS. Such interactions will occur at the discretion of the manufacturer or supplier and are intended to facilitate the submission of successful notifications because we will not accept notifications for review without adequate scientific support.

IV. References

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of December 4, 2016, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after December 4, 2016.

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