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MEMORANDUM

From: Martin J. Hahn
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Re: **FDA Issues Final Guidance on FCN Requirements for FCS in Contact with Infant Formula and Human Milk**

We are writing this memo to bring to your attention that the Food and Drug Administration (FDA) recently published a new final guidance titled: "Preparation of Food Contact Notifications for Food Contact Substances in Contact with Infant Formula and/or Human Milk" (FCN Guidance). 1/ The guidance contains recommendations regarding how the scientific information in food contact notifications (FCNs) for infant food use should demonstrate that the food contact substance (FCS) is safe for the specific intended use in contact with infant food. FDA has previously provided guidance for the safety assessment of FCSs. 2/ However, the earlier guidance document did not specifically address dietary exposure and safety assessment considerations related to the migration of chemical substances from packaging and other food contact articles as it pertains to infants. FDA meant to fill the gap with this new guidance and the FCSs that would be affected by this guidance document include infant formula packaging for liquid and powdered formula, baby bottles, bottle inserts, nipples, and any other materials that are in contact with infant food.

Below, we highlight the FDA's chemistry and toxicology recommendations: 3/

Chemistry Recommendations:

FDA has provided specific recommendations pertaining to the conditions for migration testing. Specifically, the agency noted liquid formula lawfully marketed in the United States today is primarily packaged in plastic containers or polymer-coated metal cans, which are frequently intended to be thermally treated by the manufacturer in the container. Powdered formula, on the other hand, 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. Finally, when human milk and infant formula are

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1/ 84 Fed. Reg. 20370-20371 (May 09, 2019). FDA issued the draft guidance, which is similar to the current final guidance, on December 8, 2016.

2/ *See* U.S. Food and Drug Administration, *Guidance for Industry: Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations*, April 2002, http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081825.htm); U.S. Food and Drug Administration, *Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations*, December 2007, (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081818.htm).

3/ The agency also provides "Administrative Recommendations," which are in line with the previous guidance documents and current practice.

consumed through baby bottles, some thermal treatment of the human milk or formula in the bottle such as warming of formula before feeding may occur.

Based on the above, FDA recommended the following conditions for migration testing:

Formula Type	Subtype	Recommended Test Condition
Liquid formula	For polymer-coated metal cans, where the contents are retorted in the can	Condition of use A (High temperature, heat sterilized or retorted (ca. 121 ºC (250 ºF)))
	For plastic articles where sterilization occurs outside the container	Other conditions of use
Powdered formula	-	Condition of use E (Room temperature filled and stored (no thermal treatment in the container))
Baby bottles	-	Condition of use B (Boiling water sterilized)

Notably, FDA has developed default values for both infant body weight (i.e., 6.3 kg-bw/infant) and infant food consumption (i.e., 900 g formula/infant/day) that were determined based on the 2005-2010 National Health and Nutrition Examination Survey (NHANES) food consumption survey. These values resulted in a consumption-to-mass ratio of 0.14 kg/kg bw/d.

The agency also noted the potential for elevated exposures on a body weight basis for infants because they exclusively consume human milk and/or infant formula during the first 6 months. Exposure estimates for FCSs are generally based on "Consumption Factors" and "Food-Type Distribution Factors," which are average values for all foods expected to contact specific types of packaging materials. Because infants only consumed infant foods during the first 6 months, FDA does not recommend the use of "Consumption Factors" or "Food-Type Distribution Factors" for calculating exposure to infant food.

Toxicology Recommendations

In the guidance, the agency states that additional testing or safety information beyond the recommendations in the earlier 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 evaluate whether the safety literature or the chemical structure of the FCS may indicate a potential for developmental toxicity (e.g., neurotoxicity, immunotoxicity, reproductive toxicity, or other endpoints). When designing studies and evaluating data to reduce uncertainty in the safety assessment for infant exposures, FDA recommends considering that pharmacokinetic (PK), absorption, distribution, metabolism, and excretion (ADME), toxicokinetic/toxicodynamic (TK/TD), and/or other relevant data can be incorporated to more accurately describe interspecies differences or differences between juvenile and adult animals.

FDA provides the following equations for calculating life time cancer risk (LCR):

- Risk for birth through 6 months: $R_{0\text{-}6\ mos}$ = Unit Cancer Risk (UCR) x 10 x infant exposure x (0.5yr/78yr)
- Risk for 6 months through 2 years: $R_{6\ mos\text{-}2\ yrs}$ = UCR x 10 x general population exposure x (1.5yr/78yr)
- Risk for 2 years to 78 years: $R_{2\text{-}78\ yrs}$ = UCR x general population exposure x (76yr/78yr)

- $LCR = R_{0\text{-}6\ mos} + R_{6\ mos\text{-}2\ yrs} + R_{2\text{-}78\ yrs}$ 4/

As the above equations indicate, the recommended calculations involve: (1) developing/obtaining the unit cancer risk or UCR; (2) calculating the estimated exposure for each specific population exposure; (3) developing the age-dependent adjustment factor (ADAF) based on age; and (4) calculating the percent of lifespan for each age group. LCR represents the sum of the risk from all three age periods: the 0-6 month age period, the 6 month through 2-year age period and the 2-year through 78-year age period.

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Although this guidance applies to new FCN submissions, in its "Constituent Update," the agency states that it re-reviewed a sample of effective FCNs for substances intended for use in infant formula and/or human milk packaging following the new guidance and the results affirmed that these food contact materials are safe for intended uses. 5/

We will continue to monitor this and other FDA initiatives for food packaging materials. Should you have any questions, please do not hesitate to contact us.

4/ The average lifespan age of 78 years is used in the equations and reflects the current average U.S. lifespan.

5/ *See* U.S. Food and Drug Administration, *FDA Issues Guidance on Food Contact Substances for Use with Infant Formula and/or Human Milk*, May 2019, (https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-guidance-food-contact-substances-use-infant-formula-andor-human-milk).