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Chemistry, manufacturing and exposure assessments to support generally recognized as safe (GRAS) determinations

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ABSTRACT

Identity, stability, purity, intended use levels in what foods and technical effects, and probable intake are among the key components in an assessment to support GRAS determinations. The specifications of identity of a food substance are an important component of the safety assessment as changes in the physical and chemical properties of a food substance can influence its technical effect in food and can influence its nutritional or toxicological properties of the food substance. Estimating exposure is a key determining step in the safety evaluation of a food substance. Intake assessment in GRAS determination is necessarily comprehensive based on cumulative exposure, i.e. proposed new uses plus background dietary exposure. Intake estimates for safety assurance in a GRAS determination also represent conservative overestimate of chronic exposure as they are based on 2-day average daily intake and the upper percentile (90th) intake among consumers. In contrast, in a nutrient assessment where realistic intake estimates are of interest, usual intake estimates are relied upon. It should also be noted that intake estimates for GRAS determinations are also more conservative than estimate of dietary exposure by EPA (FIFRA), where mean per capita are used to assess chronic exposure. Overall, for safety assurance, intake assessments in GRAS determinations are comprehensively cumulative and typically conservative overestimate of exposures.

1. Introduction

US Food regulations allow for a substance to be determined to be GRAS by either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food.

The determination of GRAS for a substance requires that a scientific review be conducted and that it be based on objective evidence that includes:

- the probable intake by consumers of the substance including existing and proposed uses;
- the relevant toxicological data needed to establish the substances safety at the levels of intake estimated for the existing and proposed uses;
- safety factors generally recognized in the opinion of qualified experts as appropriate to the evaluation of the scientific data for the substances; and
- other special considerations (based on the characteristics of the substance & intended uses).

The quantity and quality of scientific evidence required to form the basis for determining whether a food ingredient is GRAS, vary considerably depending upon the estimated dietary exposure to the substance and the chemical, physical, and physiological properties of the substance.

A GRAS safety determination must fully identify the substance and describe the methods of production. The chemical identity must be a part of the description and include specifications for the product.

The identity and specifications of a food substance are an important component of the safety assessment and are used to establish safe conditions of use in food. Changes in the physical and chemical properties of a food substance can influence its technical effect in food as well as its potential effects on consumers.

The substance must be identified by its name (including chemical name and a common or trade name, applicable identification numbers, such as a Chemical Abstracts Service Registry Number (CAS Reg. No.) or an Enzyme Commission Number) and by its chemical formula(e). Other parts of the identity include: source

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(when a food substance is of natural biological origin), quantitative composition, levels of impurities and contaminants. The description of the substance must also include physical and chemical properties and specifications for these properties, e.g., melting point, boiling point, specific gravity, refractive index, optical rotation, pH, solubility, reactivity, particle size, and chromatographic, spectroscopic or spectrometric data that can be used as a "fingerprint" for identification.

Estimating exposure is a key determining step in the safety evaluation of a food substance. Intake assessment in GRAS determination is necessarily comprehensive based on cumulative exposure, i.e. proposed new uses plus background dietary exposure. The exposure assessment methodologies that are used to support a GRAS determination are the focus of this paper.

2. Estimating daily intake for Safety/GRAS determination

The estimated daily intakes (EDI) of a food ingredient must be determined for the current existing regulated uses, for the proposed new uses in foods. Natural dietary background exposure, if exist, also needs to be accounted for to estimate cumulative estimated daily intakes (EDI). The methods for conducting these analyses vary depending upon the uses and the available data. Generally, the formula for determining intake is:

$$EDI = \sum_{f=1}^{F} A_f \times C_f \quad (1)$$

where:

F: denotes the total number of foods with the ingredient of interest
A_f: denotes the amount of food "f" consumed
C_f: denotes the ingredient concentration in food "f"

In determining EDIs for safety/GRAS determinations, the maximum level of use (either existing or proposed) is assumed to be present in all foods for conservative "worst case" EDIs along with estimates of consumption of the foods by consumers with high amounts of consumption. The data for estimating consumption of the foods which are allowed or proposed to be allowed to contain the substance must be determined using reliable data. That is the food consumption data to be relied upon should be representative of the population of consumers of the relevant foods. The most common database for this purpose is the National Health and Nutrition Examination Survey (NHANES, 2015) (http://www.cdc.gov/nchs/nhanes.htm). NHANES is a program of studies designed to assess the health and nutritional status of the US population. It began in the early 1960s and in 1999, it became a continuous program. The survey examines a nationally representative sample of about 5000 persons each year. Findings from this survey are used to assess the nutritional status of the US population. Information on food consumption is collected in NHANES via two 24 h dietary recalls in the dietary interview component, also known as the What We Eat In America (WWEIA). Trained dietary interviewers collect detailed information on all foods and beverages consumed by respondents in the preceding 24 h time period. A second dietary recall is administered by telephone 3–10 days after the first dietary interview, but not on the same day of the week as the first interview.

2.1. Calcium EDTA example

As an example, EDIs can be calculated for Calcium Disodium EDTA and Disodium EDTA as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products. If, the maximum proposed levels are 200 ppm in frozen corn, the EDIs are determined by estimating consumption of frozen corn and multiplying the intake by 200 ppm (Table 1).

Table 1
Estimated daily intake of EDTA from cooked sweet corn in select products by the U.S. population 2+ yr; NHANES 2003–2006, 2-day average (mg/kg bw/day).

EDTA	N	Per capita		Per user	
		Mean	90th	Mean	90th
U.S. population 2+ yr	1257	0.01	0	0.15	0.34

The consumption of cooked sweet corn shown in Table 1 is determined using NHANES for the survey years 2003–2006. Table 1 presents the EDI for the entire US population and for the population greater than 2 years of age. Cooked sweet corn intake (as well as for other foods) can be calculated for everyone in the US population (per capita) or only for those individuals who reported consuming cooked sweet corn (per user). For each population group, corn consumption can be estimated for the population average (mean) or for those individuals who consume a lot of the corn, e.g. the upper 90th percentile consumer (Table 1).

The GRAS determination requires that the intakes of the substance from the proposed use be added to existing uses. In the case of Calcium Disodium EDTA and Disodium EDTA (GRN363) (FDA, 2011) based on current approvals specified in 21 CFR 172.120[1]. Consumption is multiplied by the maximum levels of EDTA would be permitted to be used in cooked sweet corn (200 ppm).

The cumulative EDI presented in Table 2 assumes that all corn consumed from one of these food categories contained EDTA at 200 ppm and that all of the other foods contained the maximum permitted levels of Calcium Disodium EDTA and Disodium EDTA. Based on the NHANES 2003–2006 and the maximum levels consumers who represent the upper 90th percentile would consume 0.34 from sweet corn, and 1.4 mg/kg bw/day from other foods and for a total of 1.74 mg/kg bw/day. The assumptions used in these analyses – e.g. that all of the foods contain the maximum permitted level of EDTA all the time and consumers always consume high amounts of the foods, results in estimates of intake that overestimate actual cumulative total intakes. These conservative assumptions incorporate an extra "safety factor" into the GRAS determination.

In the case of Calcium Disodium EDTA and Disodium EDTA, an acceptable daily intake (ADI) has been established by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) Joint Expert Committee on Food Additives (*JECFA*) has established an ADI of 2.5 mg/kg bw/day (WHO, 1973). Even the conservative estimates presented in Table 2 for Calcium Disodium EDTA and Disodium EDTA are less than the *JECFA* ADI of 2.5 mg/

[1] Calcium disodium EDTA is approved as a food additive in 21 CFR 172.120 under limited conditions of use: as a preservative, sequestrant, flavor retention agent, color retention agent, texture retention agent, and antigushing agent at particular use levels in pickled cabbage, canned carbonated soft drinks, canned white potatoes, cooked canned clams, cooked canned crabmeat, pickled cucumbers, distilled alcoholic beverages, non-standardized dressings, cooked canned dried lima beans, hard-cooked egg products containing whites and yolk, fermented malt beverages, French dressing, cooked canned legumes, mayonnaise, cooked canned mushrooms, oleomargarine, pecan pie filling, cooked canned pink beans, potato salad, processed dry pinto beans, cooked canned red beans, salad dressing, sandwich spread, sauces, cooked canned shrimp, spice extractives in soluble carriers, and artificially colored and lemon-flavored or orange-flavored spreads. Proposed for use as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight. Calcium disodium EDTA would be employed at a maximum use level of 200 ppm and disodium EDTA at a maximum use level of 165 ppm.