§ 128.24 [Amended]

2. In § 128.24, paragraph (a) is amended by removing the reference ''$1,250'' wherever it appears and adding, in its place, the reference ''$2,000''.

PART 141—ENTRY OF MERCHANDISE

1. The authority citation for Part 141 continues to read in part as follows:

Authority: 19 U.S.C. 66, 1448, 1484, 1624.

* * * * *

Subpart F also issued under 19 U.S.C. 1481;

* * * * *

§ 141.82 [Amended]

2. In § 141.82, paragraph (d) is amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

PART 143—SPECIAL ENTRY PROCEDURES

1. The authority citation for Part 141 continues to read as follows:

Authority: 19 U.S.C. 66, 1481, 1484, 1498, 1624.

§ 143.21 [Amended]

2. In § 143.21, paragraphs (a), (b), (c), (f) and (g) are amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

§ 143.22 [Amended]

3. In § 143.22, the second sentence is amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

§ 143.23 [Amended]

4. In § 143.23, paragraphs (d) and (i) are amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

§ 143.26 [Amended]

5. In § 143.26, the heading and text of paragraph (a) are amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

PART 145—MAIL IMPORTATIONS

1. The authority citation for Part 145 continues to read in part as follows:

Authority: 19 U.S.C. 66, 1202 (General Note 20, Harmonized Tariff Schedule of the United States), 1624.

Section 145.4 also issued under 18 U.S.C. 545, 19 U.S.C. 1618;

* * * * *

Section 145.12 also issued under 19 U.S.C. 1315, 1484, 1498;

* * * * *

Section 145.35 through 145.38, 145.41, also issued under 19 U.S.C. 1498;

* * * * *

§ 145.4 [Amended]

2. In § 145.4, paragraph (c) is amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

§ 145.12 [Amended]

3. In § 145.12, paragraphs (a)(2), (a)(3) and (b)(1) and the heading and text of paragraph (c) are amended by removing the reference ''$1,250'' wherever it appears and adding, in its place, the reference ''$2,000''.

§ 145.35 [Amended]

4. Section 145.35 is amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

§ 145.41 [Amended]

5. Section 145.41 is amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

PART 148—PERSONAL DECLARATIONS AND EXEMPTIONS

1. The authority citation for Part 148 continues to read in part as follows:

Authority: 19 U.S.C. 66, 1496, 1498, 1624. The provisions of this part, except for subpart C, are also issued under 19 U.S.C. 1202 (General Note 20, Harmonized Tariff Schedule of the United States).

* * * * *

§ 148.23 [Amended]

2. In § 148.23, the heading and text of paragraph (c)(1) and the heading and introductory text of paragraph (c)(2) are amended by removing the reference ''$1,250'' and adding, in its place, the reference ''$2,000''.

Approved: March 18, 1998.

Robert S. Trotter,

Acting Commissioner of Customs.

John P. Simpson,

Deputy Assistant Secretary of the Treasury.

[FR Doc. 98–8832 Filed 4–2–98; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 87F–0086]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Sucralose

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of sucralose as a nonnutritive sweetener in food. This action is in response to a petition filed by McNeil Specialty Products Co.

DATES: The regulation is effective April 3, 1998; written objections and requests for a hearing by May 4, 1998. The Director of the Office of the Federal Register approves the incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of certain publications in § 172.831(b) (21 CFR 172.831(b)), effective April 3, 1998.

ADDRESSES: Submit written objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Blondell Anderson, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3106.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction
II. Evaluation of Safety
A. Estimated Daily Intake
B. Evaluation of Toxicological Testing Results
1. Pharmacokinetics and Metabolism
a. Comparative pharmacokinetics
b. Sucralose metabolism
2. Genotoxicity Testing
3. Reproductive/Developmental Toxicity Studies
a. Sucralose
i. Two-generation reproductive toxicity study in rats (E056)
ii. Teratology study in rats (E030)
iii. Teratology studies in rabbits (El34)
b. Sucralose hydrolysis products
i. Two-generation reproductive toxicity study in rats (E052)
ii. Teratology study in rats (E032)
c. Male fertility studies of sucralose and its hydrolysis products in rats (E016, E038, E090, and E107)
4. Chronic Toxicity/Carcinogenicity Studies
a. Sucralose
i. Combined chronic toxicity/carcinogenicity study in rats (E057)
ii. Carcinogenicity study in mice (E055)
iii. Chronic toxicity study in dogs (E051)
b. Sucralose hydrolysis products—carcinogenicity study in rats (E053)
5. Special Toxicological Studies
a. Body weight gain (E058, E130, E143, E151, E160, E161)
i. The palatability hypothesis
ii. The agency's evaluation of the palatability hypothesis
iii. Resolution of the body weight gain decrement issue

b. Immunotoxicity study in rats (E162)
c. Neurotoxicity studies in mice and monkeys (E008 and E009)
d. Diabetic Studies (E156, E157, E168, E170, E171)
C. Acceptable Daily Intake Estimate for Sucralose
III. Comments
A. Determination of No-Observed-Effect Level and ADI
1. No-Observed-Effect Level in the Chronic Toxicity Study
2. No-Observed-Effect Level in Developmental Toxicity Studies
3. Derivation of ADI
B. Immunotoxic Potential of Sucralose
C. Mutagenicity of 1,6–DCF
D. Renal Effects
E. Fetal Edema
F. Bioaccumulation
G. Antifertility Effects
H. Neurotoxicity Effects
I. Exposure to Sucralose Hydrolysis Products
J. The Need for Studies in Special Populations
K. Labeling
IV. Conclusion
V. Environmental Effects
VI. References
VII. Objections

I. Introduction

In a notice published in the **Federal Register** of May 8, 1987 (52 FR 17475), FDA announced that a food additive petition (FAP 7A3987) had been filed by McNeil Specialty Products Co. (McNeil), P.O. Box 3000, Skillman, NJ 08558–3000 proposing that the food additive regulations be amended to provide for the safe use of sucralose (1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside) as a nonnutritive sweetener in food where standards of identity do not preclude such use. (McNeil's address has since changed to 501 George St., New Brunswick, NJ 08558–3000.)

The petitioner has requested the use of sucralose in 15 food categories as described in § 170.3 (21 CFR170.3(n)) as follows: Baked goods and baking mixes (§ 170.3(n)(1)); beverages and beverage bases (nonalcoholic) (§ 170.3(n)(3)); chewing gum (§ 170.3(n)(6)); coffee and tea (§ 170.3(n)(7)); confections and frostings (§ 170.3(n)(9)); dairy product analogs (§ 170.3(n)(10)); fats and oils (§ 170.3(n)(12)); frozen dairy desserts and mixes (§ 170.3(n)(20)); fruit and water ices (§ 170.3(n)(21)); gelatins, puddings, and fillings (§ 170.3(n)(22)); jams and jellies (§ 170.3(n)(28)); milk products (§ 170.3(n)(31)); processed fruits and fruit juices (§ 170.3(n)(35)); sugar substitutes (§ 170.3(n)(42)); and sweet sauces, toppings, and syrups (§ 170.3(n)(43)). This final rule lists all of the requested uses.

Sucralose has also been referred to as trichlorogalactosucrose or 4,1′,6′-trichlorogalactosucrose. The Chemical Abstracts Service Registry number (CAS Reg. No.) for sucralose is 56038–13–2. Sucralose is a disaccharide that is made from sucrose in a five-step process that selectively substitutes three atoms of chlorine for three hydroxyl groups in the sugar molecule. It is produced at an approximate purity of 98 percent. Sucralose is a free-flowing, white crystalline solid that is soluble in water and stable both in crystalline form and in most aqueous solutions; it has a sweetness intensity that is 320 to 1,000 times that of sucrose, depending on the food application.

Hydrolysis of sucralose can occur under conditions of prolonged storage at elevated temperatures in highly acidic aqueous food products. The hydrolysis products are the monosaccharides, 4-chloro-4-deoxy-galactose (4–CG) and 1,6-dichloro-1,6-dideoxyfructose (1,6–DCF).

McNeil's original submission to FDA contained data and information from toxicity studies in several animal species, other specific tests in animals, and information from clinical tests in human volunteers. The toxicity data base included: Short-term genotoxicity tests, subchronic feeding studies, chronic toxicity/carcinogenicity studies in rats and mice, a chronic toxicity study in dogs, reproductive toxicity studies in rats, teratology studies in rats and rabbits, male fertility studies in rats, and neurotoxicity studies in mice and monkeys. Other specific tests conducted with animals included: Pharmacokinetics and metabolism studies on sucralose in several species, mineral bioavailability studies in rats, and several studies related to food consumption and palatability in rats and dogs. Human clinical testing addressed the pharmacokinetics and metabolism of sucralose, in addition to its potential effects on carbohydrate metabolism. The petitioner also submitted a report prepared by a panel of experts in various scientific disciplines who independently evaluated and critiqued the sucralose data base to identify areas of potential controversy.

During the course of the agency's evaluation of the sucralose petition, McNeil submitted additional studies that had been conducted in response to questions and concerns raised by the governmental reviewing bodies of other countries. The additional studies included a 6-month gavage study in rats, two comparative pharmacokinetics studies in rats and rabbits, an immunotoxicity feeding study in rats, and study of unscheduled deoxyribonucleic acid (DNA) synthesis.

In response to an issue raised by FDA, the petitioner submitted a 6-month sucralose feeding study in rats, with a dietary restriction design, to evaluate the toxicological significance of a body weight gain decrement effect observed in sucralose-treated rats.

In anticipation of the potential wide use of sucralose in persons with diabetes mellitus and to address concerns raised by a diabetic association group in Canada, the petitioner performed a series of clinical studies. Because of results observed in diabetic patients that were treated with sucralose in a 6-month clinical study, the petitioner requested (in 1995) that the agency withhold its final decision on the safety of sucralose until that observation could be further investigated. At that time, the petitioner initiated additional studies with the main objective of evaluating the effects sucralose would have on glucose homeostasis in patients with diabetes mellitus.

II. Evaluation of Safety

In the safety evaluation of a new food additive, the agency considers both the projected human dietary exposure to the additive and the data from toxicological tests submitted by the petitioner. Other relevant information (e.g., published literature) is also considered. The available data and information submitted in a food additive petition must establish, to a reasonable certainty, that the food additive is not harmful under the intended conditions of use.

A. Estimated Daily Intake

In determining whether the proposed use of an additive is safe, FDA typically compares an individual's estimated daily intake (EDI) of the additive to the acceptable daily intake (ADI) established from the toxicity data. The agency determines the EDI by making projections based on the amount of the additive proposed for use in particular foods and on data regarding the consumption levels of these particular foods. The proposed use levels of sucralose are supported by taste panel testing that was reported in the petition. The petitioner also submitted survey information on the consumption of the food types for which the use of sucralose was requested.

The agency commonly uses the EDI for the 90th percentile consumer of a food additive as a measure of high chronic exposure. For the requested food uses of sucralose, the agency has determined the 90th percentile EDI for consumers 2 years old and older (''all ages'') to be 98 milligrams per person per day (mg/p/d), equivalent to

approximately 1.6 mg per kilogram of body weight per day (mg/kg bw/d) (Refs. 1 and 2).

Because sucralose may hydrolyze in some food products (although only to a small extent and only under limited conditions), the resulting hydrolysis products may also be ingested by the consumer. Therefore, the agency has also calculated EDI's for the combined hydrolysis products of sucralose. The 90th percentile EDI is 285 micrograms per person per day (µg/p/d), equivalent to 4.7 µg/kg bw/d (Refs. 1 and 2).

B. Evaluation of Toxicological Testing Results

The major studies relevant to the safety decision regarding the petitioned uses of sucralose are discussed in detail in section II.B of this document. The individual studies are identified by ''E'' numbers, as designated by McNeil in the sucralose petition.

1. Pharmacokinetics and Metabolism

Studies were conducted to characterize and compare the metabolic fate of sucralose in various animal species to that seen in humans in order to assist in the selection of an appropriate animal model for safety extrapolation to humans.

a. *Comparative pharmacokinetics.* The absorption, metabolism, and elimination of sucralose have been studied in several different animal species, including humans. Based on its evaluation of these studies, the agency concludes that, in general, sucralose is poorly absorbed following ingestion, with 36 percent or less of the dose absorbed in rats (E004 and E137), mice (El46), rabbits (El24), dogs (E049 and E123), and humans (E003, E033, and E128). Although there is consistency among laboratory animal species in the routes of elimination of sucralose when administered by the intravenous route (80 percent urinary, 20 percent fecal), the amounts of sucralose absorbed and rates of elimination after oral administration differ considerably (Ref. 3). The agency estimates that about 5 percent of the ingested dose is absorbed from the gastrointestinal system of rats, while that in rabbits and mice ranged from 20 to 33 percent. Gastrointestinal absorption of sucralose by the dog was in the range of 33 to 36 percent. Studies in human male volunteers showed absorption values in the range of 11 to 27 percent, which is between the ranges observed for rats (lower bound) and rabbits and mice (upper bound). In all of the species tested, plasma disappearance curves are biphasic (E003, E004, E049, E123, E128, E146, El63, and E164). With the exception of the rabbit (El64), these curves are dominated by phase 1, with a half-life of 2 to 5 hours. In the rabbit elimination is dominated by phase 2, with a half-life of 36 hours (El64) (Ref. 3). The longer half-life of sucralose in the rabbit was initially thought to be the result of reingestion of sucralose. However, study E164, which was specifically designed to address this question by controlling coprophagia, indicated that sucralose elimination is intrinsically slower from the rabbit than from other species tested (Refs. 3 and 4). Therefore, the agency concludes that the pharmacokinetics of sucralose in the rabbit is significantly different from that in humans and other tested species.

b. *Sucralose metabolism.* The majority of ingested sucralose is excreted unchanged in the feces and most of what is absorbed appears unchanged in the urine, with only minor amounts appearing as metabolites (Refs. 3, 4, and 5). Mice (El46) and rats (El37) were found to metabolize less than 10 percent of the absorbed sucralose, while rabbits (El24) (20 to 30 percent), humans (El38 and E145) (20 to 30 percent), and dogs (El33) (30 to 40 percent) metabolize greater quantities of the absorbed sucralose. Results from the submitted animal and human pharmacokinetics data identified three major sucralose metabolites (Ml, M2, and M3) in urine in addition to unchanged sucralose. The metabolic profile of sucralose in rats was qualitatively similar to that seen in humans. In addition to unchanged sucralose, two sucralose metabolites, Ml and M2, were detected in the urine of rats and humans after oral dosing of sucralose. The metabolic profile of mice for sucralose differed from that of humans and the other tested animals (rats, dogs, and rabbits) in that a unique urinary metabolite, M3, was identified in addition to the presence of the Ml (trace amounts) and M2 metabolites. A pronounced difference was observed in the proportions of M2 and M3 excreted by male versus female mice: Males produced more M2 than M3, while the opposite was true of female mice. The metabolic profile of the rabbit for sucralose also showed differences when compared to that seen in humans, rats, mice, or dogs. In addition to unchanged sucralose, a small number of unidentified metabolites (more polar than sucralose) were observed in rabbit urine, but were not characterized (Refs. 3, 6 and 7). Dogs produced primarily the M2 metabolite and only a trace amount of the Ml metabolite.

After repeated dosing, there was no evidence that sucralose induced microsomal enzymes in rats (El44) (Ref. 7). There was also no evidence of metabolic adaptation following chronic dosing with sucralose in rats (E057e) (Ref. 3).

Based on the submitted pharmacokinetics data, the agency concludes that the rabbit metabolism of sucralose is notably different from that of humans in two important aspects: (1) A longer sucralose plasma half-life, and (2) the presence of unique urinary sucralose metabolites. Although pharmacokinetic differences between the other tested animals (rats, mice, and dogs) and humans were not as pronounced, the profile for rats was most similar to that for humans. The agency discusses the relevance of these data for the selection of an appropriate animal model in section II.C of this document.

2. Genotoxicity Testing

Sucralose and its hydrolysis products were tested in several in vitro and short-term in vivo genotoxicity tests. In the absence of bioassay data, such tests are often used to predict the carcinogenic potential of the test compound. However, in the case of sucralose and its hydrolysis products, chronic toxicity/carcinogenicity bioassay data are also available.

Sucralose was shown to be nonmutagenic in an Ames test (E0ll) and a rat bone marrow cytogenetic test (E013). Tests for the clastogenic activity of sucralose in a mouse micronucleus test (E0l4) and a chromosomal aberration test in cultured human lymphocytes (E012) were inconclusive. Sucralose was weakly mutagenic in a mouse lymphoma mutation assay (E014).

The hydrolysis product, 4–CG, was nonmutagenic in the Ames test (E025) and mouse lymphoma assay (E026). 4–CG was nonclastogenic in the chromosomal aberration assay (E0I2). Other assays (human lymphocytes (E012), rat bone marrow (E027)) were inconclusive. Thus, no test on 4–CG produced a genotoxic response.

The other hydrolysis product, 1,6–DCF, was not clastogenic in the chromosomal aberration assay in rat bone marrow (E019). Results of three other genotoxic tests were inconclusive: The chromosomal aberration assay in cultured human lymphocytes (E012), the sex-linked recessive lethal assay in *Drosophila melanogaster* (E021), and the covalent DNA binding potential study in rats (El48). 1,6–DCF was weakly mutagenic in the Ames test (E020) and the L5178Y TK+/− assay (EO22 and E024). In an unscheduled DNA synthesis study (El65), 1,6–DCF did not induce DNA repair synthesis in isolated rat hepatocytes.

An equimolar mixture of the hydrolysis products was not genotoxic in the in vivo sister chromatid exchange assay in mice (E150) and was inconclusive in a dominant lethal (mouse) test (E034).

As the foregoing discussion reflects, both sucralose and its hydrolysis products showed weakly genotoxic responses in some of the genotoxicity tests. More importantly, however, as demonstrated in the 2-year rodent bioassays (E053, E055, and E057), there was no evidence of carcinogenic activity for either sucralose or its hydrolysis products as discussed in sections II.B.4.a.i, II.B.4.a.ii, and II.B.4.b.i of this document. Results from these chronic carcinogenicity studies supersede the results observed in the genotoxicity tests because they are more direct and complete tests of carcinogenic potential (Refs. 5, 6, 8, 9, and 10).

3. Reproductive/Developmental Toxicity Studies.

Studies were performed in order to evaluate the toxic potential of sucralose and its hydrolysis products on the reproductive systems of mature male and female rats as well as on the postnatal maturation of reproductive functions of offspring through two successive generations. The objective of the teratology studies was to determine the potential effects of sucralose and its hydrolysis products on the developing fetus.

a. *Sucralose*—i. *Two-generation reproductive toxicity study in rats (E056).* In this study, groups of 30 male and 30 female rats of the Sprague-Dawley CD strain were fed sucralose at dose levels of 0.3, 1.0, and 3.0 percent in the diet 10 weeks prior to breeding and throughout two successive generations.

No treatment-related effects on any of the reproductive endpoints (estrous cycles, mating performance, fertility index, gestation length, gestation index) were observed in either generation. Litter size and offspring viability were also unaffected by sucralose treatment. Decreases in body weight gain of 11 to 25 percent and 2 to 12 percent for adult rats were observed during both premating periods for the first (F_1) and second (F_2) generations, respectively. Slightly decreased food intake was also observed for both generations (F_0, 5 to 9 percent; F_1, 3 to 5 percent).

Although significant decreases in the relative thymic weights were noted in the F_0 (male and female) and the F_1 (male and female) rats in this study after dietary administration of sucralose at the high-dose (3 percent) level, because of the nature of the experimental design for reproductive studies, the agency cannot evaluate the toxicological significance of this observation in this study. Thymic and other lymphoidal effects are more appropriately evaluated in immunologic studies that are designed to examine directly parameters of immunologic functions. Such immunotoxicity studies on sucralose are discussed in section II.B.5.b of this document.

Based upon the results of study E056, the agency concludes that sucralose does not cause any reproductive effects in rats in doses up to 3 percent in the diet (Refs. 5, 10, 11, and 12).

ii. *Teratology study in rats (E030).* Sucralose was administered by gavage to groups of 20 pregnant Sprague Dawley CD rats at dose levels of 500, 1,000, and 2,000 mg/kg bw/d from day 6 through day 15 of gestation.

No treatment-related effects were noted in the dams at necropsy with respect to the number of implantation sites, pre-implantation losses, or post-implantation losses. The number of live young, as well as fetal and placental weights, were also unaffected by treatment. Neither body weight gain nor food consumption were affected by treatment with sucralose.

Based upon the results of E030, the agency concludes that sucralose did not cause maternal toxicity, embryo toxicity, or fetal toxicity; nor did sucralose induce terata in rats at dose levels up to 2000 mg/kg bw/d (Refs. 5 and 13).

iii. *Teratology study in rabbits (El34).* Sucralose was administered by gavage to groups of 16 to 18 pregnant rabbits at dose levels of 0, 175, 350, and 700 mg/kg/d during days 6 to 19 of gestation. Uterine contents of the females were examined at termination of the study (day 29 of gestation).

A total of 11 rabbits (1 in the control group, 4 in the 175 mg/kg bw/d group, 2 in the 350 mg/kg bw/d group, and 4 in the 700 mg/kg bw/d group) died or were killed in extremis (near death) because of reasons unrelated to treatment. Two deaths occurred in the high-dose (700 mg/kg bw/d) group that the agency considers treatment-related because they were associated with symptoms (weight loss and reduced food intake) occurring only at the highest dose. Three of the 12 surviving rabbits in the high-dose group were eliminated from the study because they did not become pregnant.

From the remaining nine pregnant rabbits in the high-dose group only five animals successfully carried to term and produced viable young. The other four females in this group aborted their fetuses. Decreases in the mean number of viable young per litter were also observed in this group. The mean number of post-implantation losses also increased. Gastrointestinal tract disturbances were noted in high-dose rabbits. These effects observed at the high-dose level were not seen at either low- or mid-dose levels (Refs. 5, 14, and 15). While maternal and fetal toxicity were observed at the high-dose level, there was no evidence of frank terata at any of the tested dose levels. Thus this study demonstrates that sucralose is not teratogenic in rabbits.

b. *Sucralose hydrolysis products*—i. *Two-generation reproductive toxicity study in rats (E052).* Groups of 30 male and 30 female Sprague-Dawley CD rats were fed an equimolar mixture of the sucralose hydrolysis products (4–CG and 1,6–DCF) at dose levels of 0, 200, 600, and 2,000 parts per million (ppm) in the diet for 10 weeks prior to breeding and through two successive generations.

No treatment-related effects on estrus cycles, mating performance, fertility, length of gestation, litter size, and offspring viability were observed in either generation (F_0 or F_1 generation). During the 10-week premating period for both generations, body weight gain of males was significantly reduced in the high-dose (2,000 ppm) group only. Body weight gain of females was significantly reduced in all treatment groups during this same period of time. Decreased food intake was observed in the high-dose males and females of the F_0 generation. In both generations, reduction in weight gain was observed in females during pregnancy and in offspring from birth to weaning. No effect other than reduced body weight gain was related to treatment (Refs. 5, 10, 14, and 16).

The agency concludes that the administration of the sucralose hydrolysis products in the rat diet at levels up to 2,000 ppm caused no alteration in the reproductive performance of the animals over two generations (Refs. 5 and 16).

ii. *Teratology study in rats (E032).* An equimolar mixture of the sucralose hydrolysis products was administered by gavage to groups of 20 pregnant Sprague-Dawley rats at dose levels of 30, 90, and 270 mg/kg bw/d, from day 6 to 15 of gestation. The study was terminated on day 21 of gestation.

Results from this study showed no dose-related increase in the incidence of terata among treated groups. Body weight gain of dams in the high-dose group (270 mg/kg bw/d) was significantly reduced, whereas weight gains in the low- and mid-dose dams were comparable to controls. Decreased

fetal body weights and placental weights were observed at the high dose.

The agency concludes that the sucralose hydrolysis products did not produce terata in rats when administered at doses up to 270 mg/kg bw/d (Refs. 10 and 13).

c. *Male fertility studies on sucralose and its hydrolysis products in rats (E016, E038, E090, and E107).* Some chlorinated monosaccharides have been reported to affect male fertility in rats by interfering with spermatogenesis (Ref. 17). McNeil noted the structural similarity of such compounds to the hydrolysis products of sucralose, and submitted a series of antifertility studies on a series of chlorinated sugars, including sucralose.

All of the studies were of similar design. Groups of male rats were exposed for 14 days either by gavage or in the diet to 300 micromoles (μmol) of either sucralose or one of the chlorosucrose compounds mentioned above. The antifertility compound, 6-chloro-6-deoxyglucose, was used as the positive control in these studies. Treated male and untreated female rats were mated 1 and 2 weeks after treatment. Male mating performance and fertility were observed.

The agency has reviewed these studies and observes that the studies were too short to cover the full cycle of spermatogenesis in rats (Refs. 5 and 18). Because of their short duration, FDA concludes that these studies, considered alone, are insufficient to assess the antifertility potential of sucralose in male rats (Refs. 5 and 18). However, the agency believes that further testing is not necessary because the results from the two-generation reproduction studies adequately address any toxicological concerns regarding the potential antifertility effects of sucralose and its hydrolysis products. As discussed previously, in the two-generation reproduction studies (E052 and E056), in which sucralose or its hydrolysis products were fed to rats, no effects on fertility or other reproductive parameters were observed in either male or female rats (see sections II.B.3.a.i and II.B.3.b.i. of this document).

4. Chronic Toxicity/Carcinogenicity Studies

A combined chronic toxicity/carcinogenicity study (E057) in rats and a carcinogenicity study in mice (E055) were conducted to study the chronic toxicity and carcinogenic potential of sucralose when administered to rodents over most of their lifetime. Because human exposure to sucralose could possibly occur during in utero development, an in utero phase was included in the rat study. A chronic (1-year) study on sucralose was also performed in dogs (E051) in order to assess the effects of sucralose administration in a nonrodent species. In addition, a 2-year carcinogenicity study in rats (E053) was carried out to study the chronic toxicity and carcinogenic potential of sucralose hydrolysis products.

a. *Sucralose*—i. *Combined chronic toxicity/carcinogenicity study in rats (E057).* This study consisted of a breeding phase, a carcinogenicity phase, and a chronic toxicity phase. The carcinogenicity and chronic toxicity phases were concurrently performed in this study. The breeding phase of this study examined the potential in utero effects of sucralose during development. During this phase parental (F_0) Sprague-Dawley CD rats, 70 males and 70 females per group, were fed diets containing 0, 0.3, 1, or 3 percent sucralose for a 4-week period prior to mating and during gestation. One male and one female weanling pup were selected from each of 50 litters and allocated to the appropriate group of the carcinogenicity phase. Additional rats (30 per sex per group) were selected for the chronic toxicity phase of this study.

Rats in each of the groups of this study were gang-housed, five animals per sex per cage. After 52 weeks of sucralose treatment, an interim sacrifice was performed on 15 males and 15 females from each group of the chronic toxicity phase of the study. The remaining surviving rats in this phase of the study were sacrificed at treatment week 78. In the carcinogenicity phase, surviving rats were sacrificed at week 104. In both phases of the study, classic toxicological parameters such as mortality, body weight, hematology, clinical chemistry, and organ weights were examined in treated and control rats. Food consumption was calculated weekly from the total weight of food consumed by each cage of rats. Histopathological examinations were performed on representative tissues from control and high-dose rats.

Sucralose treatment had no effect on reproductive performance or on fertility of the parental rats during the breeding phase. In both the chronic toxicity and carcinogenicity phases of the study, survival of rats was unaffected by sucralose treatment.

In the carcinogenicity phase, there was no evidence of treatment-related neoplasia in any of the rats (Ref. 19). McNeil reported an apparent increased incidence of male rats with hepatocellular clear cell foci. FDA pathologists reviewed the liver histopathology slides from this study that were obtained from McNeil. The agency's pathologists observed that the increase in the incidence of male rats with hepatocellular clear cell foci was only marginal and that there was no concomitant increase in the severity of this lesion among the treated animals. Therefore, the agency concludes that the occurrence of hepatocellular clear cell foci was incidental and not treatment-related (Refs. 5 and 20).

Renal pelvic mineralization and epithelial hyperplasia were noted at higher incidences among treated rats in both the chronic toxicity and the carcinogenicity phases of study E057. These changes were observed primarily in the high-dose females. The degree of severity of these lesions was reported as minimal or slight. McNeil concluded that these changes are of no toxicological significance.

FDA evaluated these changes and noted that: (1) It is not unusual to observe such lesions in aged rats, especially in females (Ref. 21). In this study (E057), the rats were at or near the end of their expected lifetime at the time of sacrifice; and (2) mineralization of the renal pelvis represents a physiological adaptation secondary to cecal enlargement. Cecal enlargement is often seen with other substances that are poorly absorbed in the upper intestine and can be expected in a study like this with a poorly absorbed substance like sucralose (Refs. 21, 22, 23, 25, and 26). Based on the previously mentioned reasons, FDA concludes that the renal pelvic mineralization and epithelial hyperplasia observed are of no toxicological significance (Refs. 6 and 26).

Decreased body weight gain was observed in all sucralose treated animals in both the carcinogenicity and chronic toxicity phases of this study. At the end of the carcinogenicity phase, mean body weight gain in sucralose-fed rats was 13 to 26 percent less than that of the control group. Food consumption in the treated groups during this phase was 5 to 11 percent less than that of the control values. At the end of the chronic toxicity phase, a reduction of 12 to 25 percent in the body weight gain was observed in the treated rats relative to controls, whereas food intake in the treated rats was reduced only 5 to 10 percent compared to controls.

McNeil postulated that this body weight gain decrement effect was the result of reduced palatability of sucralose-containing diets. However, based on the data in this study, as well as in all other rat studies in the sucralose petition, the agency was unable to conclude that reduced palatability, which affected food

consumption, fully accounted for the decreased body weight gain observed in sucralose-fed rats (Ref. 27). Thus, the agency recommended that McNeil perform additional testing to resolve the body weight gain issue (Ref. 28). In the absence of such testing, FDA could not determine a no-observed-effect level for this study (E057). The body weight gain issue is discussed in detail in section II.B.5.a of this document.

ii. *Carcinogenicity study in mice (E055).* In this study, Charles River CD–1 mice, 52 animals per sex per group, were gang-caged (4 mice per cage) and fed sucralose at 0, 0.3, 1.0, and 3.0 percent in the diet for 104 weeks. At the termination of the study, survival and classic toxicological parameters were examined for treated and control mice.

Survival rates were comparable for control and treated groups. Mean body weight gains in both male and female mice in the high dose (3 percent) group were significantly reduced (21 to 25 percent) relative to controls for the 104-week treatment period, without any significant decreases in food consumption. Of other toxicological parameters examined, significant decreases were observed only in the erythrocyte counts of females in the high-dose group. There was no evidence of treatment-related neoplasia in any of the sucralose-treated groups (Ref. 19).

Based on the effects seen on body weight gain and the erythrocytic counts at the high-dose level, the agency concludes that a dietary level of 1 percent (equivalent to 1,500 mg/kg bw/d) was the no-observed-effect level for sucralose (Refs. 5 and 29).

iii. *Chronic toxicity study in dogs (E051).* Groups of four male and four female beagle dogs were fed sucralose at concentrations of 0, 0.3, 1.0, and 3.0 percent in the diet for 52 weeks. Parameters examined in this study included mortality, body weight, food consumption, hematology, clinical chemistry, urinalysis, and histopathology.

An increase in body weight gain of sucralose-treated male dogs relative to controls was observed at all dose levels. However, this increase in weight gain was accompanied by a general increase in food consumption. All other parameters examined in this study were comparable between treated and control animals.

Because there were no toxic effects seen at any dose tested, the agency concludes that a dietary level of 3 percent (equivalent to 750 mg/kg bw/d) is the no-observed-effect level for sucralose in dogs (Refs. 5 and 30).

b. *Sucralose hydrolysis products—carcinogenicity study in rats (E053).* In this study, groups of 50 male and 50 female Sprague-Dawley CD rats were administered an equimolar mixture of the hydrolysis products (4–CG and 1,6–DCF) at concentrations of 0, 200, 600, and 2,000 ppm in the diet for 104 weeks.

There was no evidence of treatment-related neoplasia in any of the dose groups in this study. A marginal increase in the incidence of hepatocellular clear cell foci was reported in treated male and female rats. The agency determined, however, that this was not a treatment-related effect because there was no concomitant increase in severity of the hepatic lesion (Refs. 19 and 20). Thus, the agency concludes that the sucralose hydrolysis products are not carcinogenic to Sprague-Dawley CD rats when administered as an equimolar mixture in the diet at concentrations up to 2,000 ppm (Refs. 5, 19, and 31).

In this study, the mean body weight gain of the high-dose females was significantly decreased (24 percent) relative to the control mean after 104 weeks of treatment. Mean food consumption in these females over the 104-week period was also reduced 14 percent compared to the control group. The agency could not determine whether the body weight gain decrement observed at the high-dose level in this study was fully accounted for by decreased food intake. Therefore, the agency concludes that, in rats, the mid-dose (600 ppm equivalent to 30 mg/kg bw/d) is the no-observed-effect level for the hydrolysis products of sucralose (Refs. 5 and 10).

5. Special Toxicological Studies

a. *Body weight gain.* As noted previously, the agency's review of the rat data submitted in the original petition raised questions regarding the effect of sucralose on body weight gain (Ref. 27). Sucralose-fed rats in the subchronic and chronic studies showed significant decreases in body weight gain with only small reductions in food consumption (Ref. 27).

In particular, in the combined chronic toxicity/carcinogenicity rat study (E057), decreases of 13 to 26 percent in body weight gain were observed in sucralose-fed rats that had reductions in food consumption of only 5 to 11 percent compared to controls (Ref. 27). Although the treated rats ate less food, the reductions in food intake did not appear to account fully for the decreased weight gain. McNeil contended primarily that reduced palatability of the sucralose-containing diet caused treated animals to eat less and thus gain less weight. McNeil stated that, collectively, data obtained from the sucralose acceptability study (El30 and E143), sucralose pair-feeding study (E058), gavage study (El5l), and a diet spillage study (El54) supported their claim that palatability fully accounted for the reduced body weight gain (Ref. 32). Finally, McNeil also contended that this effect was neither a toxic effect nor biologically significant. The studies upon which McNeil relied are discussed followed by the agency's discussion of its evaluation of those studies.

i. *The Palatability hypothesis*—(1) *Acceptability studies in rats (El30 and E143).* Several studies were conducted to evaluate the acceptability and palatability of sucralose when administered to rats via drinking water or in the diet. Data from these rat studies showed that sucralose was acceptable in drinking water at levels up to 3,200 ppm. However, reduced food consumption was seen in rats that were administered sucralose in the diet at levels greater than 800 ppm.

(2) *Pair-feeding study in rats (E058).* Pair-feeding is an experimental procedure where two groups of animals are fed the same amount of diet. Thus, if there are differences in the body weight gain of these two groups of animals, it is due to an effect of the test substance and not due to differences in the amount of food consumed by the two groups of animals.

There were five groups of female Sprague-Dawley CD rats in this study. Initially, rats were grouped into various categories on the bases of body weight. Twenty rats were randomly selected from each of the weight categories and assigned to each of the five groups. One group was fed 3 percent sucralose in the diet (unrestricted access) for 8 weeks. Animals in the pair-fed group were fed a daily amount of basal diet equivalent to the mean food intake consumed on the previous day by the 3-percent sucralose dose group. In a third group, an ad libitum control group, rats received unrestricted access to basal diet. A fourth group was administered sucralose by gavage in amounts equivalent to that fed in the 3-percent dietary group. A fifth group served as a control group for the sucralose-gavaged rats and received distilled water by gavage.

Significant decreases in food consumption and body weight gain were observed in both the 3-percent dietary administration group and its pair-fed control group relative to ad libitum controls. Rats dosed with sucralose by gavage consumed significantly more food and gained significantly more weight than those receiving the water control.

(3) *4- to 13-week sucralose oral gavage study in rats (El5l).* Because administration by gavage circumvents effects due to dietary administration of an unpalatable test material, McNeil performed a study to investigate the effects of sucralose in rats, when administered by gavage. In this study, groups of Sprague-Dawley rats, 10 per sex per group, were administered sucralose at doses of 2,000 mg/kg bw/d for 13 weeks, 3,000 mg/kg bw/d for 9 weeks, or 4,000 mg/kg bw/d for 4 weeks. Control rats (10 to 15 per sex) were sacrificed concurrently at each of the time intervals along with the sucralose-treated rats.

There were no treatment-related gross or histopathological changes observed nor effects noted for urine and clinical chemistry parameters. The average food consumption for all sucralose dosed rats was consistently greater than that of the controls (104 to 108 percent of the controls). Mean final body weights were also greater in the sucralose treated rats compared to controls (103 to 109 percent).

(4) *Diet spillage study in rats (El54).* McNeil performed a study to determine whether the decreased body weight gain observed in several of the rat studies, including the combined chronic toxicity/carcinogenicity study, was due, in part, to increased spillage of sucralose-containing diet. If there was greater spillage of the sucralose-containing diet than that seen in controls, then the sucralose-treated animals were eating even less than they appeared to consume. In this 8-week study, three groups of Sprague-Dawley rats (15 per sex per group) were individually housed and fed either basal diet or basal diet containing sucralose at dose levels of 3 percent or 5 percent. Although overall diet spillage was significantly higher in the sucralose-treated rats compared to controls, this difference existed only for the first 2 weeks. Treated rats (both sexes) consumed 5 to 8 percent less food than controls. This decreased food intake was associated with a 10 to 15 percent depression in weight gain.

ii. *The agency's evaluation of the palatability hypothesis.* From its interpretation of the data in the acceptability studies (EI30 and E143), pair-feeding study (E058), gavage study (El5l), and diet spillage study (El54), McNeil identified three factors that the company believed led to the decrement in body weight gain observed in the combined chronic toxicity/carcinogenicity study in rats (E057): (1) Decreased food consumption due to poor palatability and increased spillage of the sucralose-containing diet; (2) inhibition of growth potential in sucralose-fed F_1 generation rats due to decreased initial body weight resulting from decreased maternal weights of the treated rats; and (3) magnification of the body weight gain effect with increases in study duration.

While the agency accepted the physiological and nutritional principles presented by McNeil, the agency concluded that McNeil's arguments did not explain fully the magnitude of the decrement in body weight gain in the sucralose-fed rats of the combined chronic toxicity/carcinogenicity study (E057) for the following reasons.

The agency disagreed with the petitioner's contention that in the combined chronic toxicity/carcinogenicity study (E057), a consistent decrease in food consumption was demonstrated at all dose levels. The agency determined that this study (E057) did not adequately measure food consumption and did not adequately account for diet spillage. Furthermore, the agency determined that in many of the sucralose rat studies food consumption decreases were not of sufficient magnitude to account for the observed body weight gain decrements seen in the sucralose-fed rats of these studies (Ref. 27). Inadequacies in the measuring of food consumption and the monitoring of spilled diets also confounded the interpretation of the pair-feeding study (E058) (Refs. 10 and 27).

The agency also disagreed that decreased initial body weights accounted for the weight gain decrement in sucralose treated rats in study E057. Although maternal weights were slightly decreased (93 to 97 percent of controls) on day 1 of lactation, this small difference was not large enough to sufficiently explain the body weight differences of the lactating pups (Ref. 27). In fact, maternal weights of the sucralose-fed rats were not significantly different from those of the control rats during days 14 to 21 of lactation (Ref. 27). Differences in initial body weights of the F_1 pups (4 to 8 percent decreases) of the combined chronic/carcinogenicity study (E057) were not sufficient to explain the magnitude of the final body weight gain decrements of these rats (Ref. 27).

Finally, although FDA agreed with the general principle that long-term food intake disparity will result in increasing differences in body weight gain over time, FDA concluded that this principle alone did not account for the degree of magnification of body weight gain decrement compared to the small reductions in food consumption seen in the sucralose studies (Ref. 27).

Based on the foregoing reasoning, FDA concluded that the acceptability studies (El30 and E143), pair-feeding study (E058), 4- to 13-week gavage study (El5l), and the diet spillage study (El54) did not adequately explain the magnitude of decreased body weight gain relative to the level of reduced food consumption, in the combined chronic/carcinogenicity study (E057). The agency thus concluded that McNeil had failed to explain satisfactorily the observed body weight gain decrement and that additional study data were needed to resolve this issue (Ref. 28). McNeil subsequently conducted two studies (E160 and E161) in rats to resolve the body weight gain decrement issue.

iii. *Resolution of the body weight gain decrement issue*—(1) *Sucralose dietary administration and dietary restriction study in rats (El60).* McNeil agreed to perform an additional sucralose feeding study (the diet restriction study, E160) to attempt to resolve the body weight gain decrement issue and to test the petitioner's palatability hypothesis. The specific purpose of the study was twofold: To determine whether the weight gain decrement observed in the sucralose-fed rats of the combined chronic toxicity/carcinogenicity study (E057) could be explained solely by decreased food consumption; and to establish a ''no-observed-effect'' level for the body weight gain decrement effect after chronic administration of sucralose.

In study E160, Sprague-Dawley CD rats were divided into eight groups (20 animals per sex per group). Three groups were fed ad libitum basal diet that contained 0, 1, or 3 percent sucralose. Three groups were fed restricted amounts of basal diet at levels that were 85, 90, or 95 percent of that eaten by the ad libitum controls. Two other groups were fed restricted diets (90 percent of ad libitum controls) that also contained sucralose at a concentration of 1 percent or 3 percent. The groups were as follows:

- Group 1 Control—basal diet ad libitum
- Group 2 Control—basal diet 95 percent of Group 1
- Group 3 Control—basal diet 90 percent of Group I
- Group 4 Control—basal diet 85 percent of Group 1
- Group 5 1-percent sucralose—ad libitum
- Group 6 3-percent sucralose—ad libitum
- Group 7 1-percent sucralose—90 percent of Group 1
- Group 8 3-percent sucralose—90 percent of Group I

Special experimental designs, including single-housing of the test animals, accurate weighing of spilled diet, and utilization of special feed jars, were incorporated into this study to ensure the highest level of accuracy in the measuring and reporting of food intake. Body weight, body weight gain, food consumption, and food conversion efficiency data were collected for each of the groups. Overall survival was unaffected by the feeding of sucralose at doses up to 3 percent for the duration of the study. The agency evaluated the data from this study using two separate statistical procedures. In the first comparison, data from control groups 1 to 4 were combined and fitted (separately for males and females) with a polynomial regression model that showed final body weight gain as a function of initial body weight and food consumption. Data for each of the sucralose groups were also fitted with this mathematical model and compared to the data from the combined control groups.

In the second comparison, mean food consumption was calculated for each sucralose group. Using the regression models, FDA calculated the expected body weight gain for animals at the mean food consumption for both the combined control groups and the sucralose groups. The calculated body weight for each sucralose group was then compared to the combined control group at the mean food consumption.

For both sexes, with both statistical procedures, the 3-percent sucralose groups (Groups 6 and 8) showed significant decrements in body weight gain relative to the combined control groups (Ref. 33). Decrements of 3.9 to 6.3 percent were observed in the mean body weights of the 3-percent sucralose-fed groups after adjustment for food consumption and initial body weight differences. Thus food consumption only partially accounted for the weight gain decrement observed in the 3-percent sucralose-fed rats. Weight decrements in the males of the 3-percent dose group stabilized by 15 weeks; in the females, differences stabilized at 20 weeks. Therefore, FDA concludes that the duration of this study (26 weeks) was sufficient to evaluate weight gain decrement effects.

In both the 1-percent sucralose group and the 1-percent sucralose with l0-percent diet restriction group, adjusted mean body weights were comparable to those of the combined control data (Ref. 33). Therefore, FDA determined that reduced food consumption accounted fully for weight gain differences in the 1-percent sucralose-fed group.

Based upon the data from this study, the agency concludes that treatment with sucralose at 1 percent in the diet had no effect on body weight gain in rats. The same data establish that rats fed sucralose at a concentration of 3 percent of the diet did show significant decreases in weight gain which were attributable to the test substance. The agency further concludes that, based upon this study, the 1-percent dose level (equivalent to the 500 mg/kg bw/d dose in study E057) is the no-observed-effect level for the body weight gain effect observed in sucralose-treated rats in this study (Ref. 34).

(2) *Sucralose toxicity study by oral (gavage) administration to Sprague-Dawley CD rats for 26-weeks (El6l).* McNeil submitted a 26-week gavage study (El6l) in rats that was designed to: (1) Provide further support for their contention that the body weight gain decrement seen in sucralose fed rats could be explained solely by decreased food intake caused by the reduced palatability of sucralose-containing diet; (2) confirm the data in the 4- to 13-week sucralose oral gavage study (EI51); and (3) to address inadequacies in the experimental design of the 4- to 13-week sucralose oral gavage study (El5l).

In this 26-week study, sucralose was administered orally to Sprague-Dawley CD rats, 20 rats per sex per group, by gavage at dosages of 0, 750, 1,500, or 3,000 mg/kg bw/d. Rats in the control group were gavaged with purified water. Body weight, water consumption, and food consumption data were recorded for all groups. Routine hematological and clinical chemistry parameters were measured. Organ weight data also were recorded. Histopathological examinations were performed on representative vital tissues from the control and high-dose groups. Histopathological examinations were performed also on all abnormal tissues.

Seven deaths occurred during the study that were attributed either to spontaneous causes not related to treatment or technical trauma during dosing: 2 males, 0 mg/kg bw/d dose; 1 male and 2 females, 1,500 mg/kg bw/d dose; and 1 male and 1 female, 3,000 mg/kg bw/d dose. Overall body weights of the animals in the sucralose-treated groups were not significantly different from those of the control group during the length of the study. The mean food consumption in the sucralose-gavaged rats was similar to that seen in the controls, except in the high-dose males. Food intake for the high-dose males was 3.9 percent greater than that of the control rats.

After making adjustments for initial body weight and food consumption, the agency performed a statistical analysis on the final body weight data using polynomial regression analysis. This analysis showed that the adjusted final body weight of the high-dose males was significantly decreased (4.6 percent; $p = 0.035$) relative to that of the control group. The adjusted mean body weights of all other groups were not significantly different from the controls.

Water consumption was significantly increased in the sucralose-treated rats relative to controls. There were no treatment-related effects seen in any of the hematological or clinical chemistry parameters tested. Cecal enlargement was the only effect of sucralose that was dose-related among both sexes of the sucralose-gavaged rats. As discussed previously in section II.B.4.i of this document, this effect is a normal physiological adaptation to poorly absorbed dietary components and not related to toxicity. The relative kidney weight of the high-dose group also was significantly increased when compared to the control group. However, this kidney effect was not associated with any toxicologically significant renal histopathology. Additionally, the plasma electrolytes of the sucralose-treated rats in this study were comparable to that seen in control animals.

As with the diet restriction study (El60), decreased body weight gain was observed in the sucralose-treated rats of the high-dose group. The agency concludes that the mid-dose (1,500 mg/kg bw/d) is the no-observed-effect level for the body weight gain effect observed in this study (El6l) (Refs. 35 and 36).

b. *Immunotoxicity study in rats.* As reported by McNeil and as noted in the agency's review of the sucralose data, thymus, spleen, and hematological changes were observed in rats at the high-dose levels in some of the short-term and long-term sucralose feeding studies. For example, when rats were fed sucralose in a 4- to 8-week range-finding study (E031) the following effects were noted: Decreased thymus and spleen weights, lymphocytopenia, and cortical hypoplasia of the spleen and thymus. In the two-generation reproductive toxicity study (E056), decreased thymus weights were noted in the F_0 and F_1 generations of the high-dose sucralose (3 percent in the diet) group. McNeil stated that the above effects were secondary to the palatability-related reduction in food consumption in treated rats.

In an effort to provide more specific and detailed assessment of the immunotoxic potential of sucralose, the petitioner conducted a 28-day oral immunotoxicity study (El62) of

sucralose in rats. In this study, groups of male and female Sprague-Dawley rats (13 per sex per group) were administered sucralose by gavage at dose levels of 750, 1,500, and 3,000 mg/kg bw/d for 28 days. Additional groups (13 per sex per group) of rats formed a gavage control group, an ad libitum diet control group, a dietary sucralose (3,000 mg/kg bw/d) group, and a diet restricted (90 percent of ad libitum control) group.

Immunotoxicological parameters examined in this study were: Thymus and spleen weights at study termination; standard histopathology evaluation of the spleen, thymus, bone marrow, and lymph nodes; and total and differential white blood cell counts. The study also examined the following specific immunologic parameters: Bone marrow cellularity, immunoglobulin subtypes, splenic lymphocyte subsets, and splenic natural killer cell activity.

Significant decreases were observed in the mean thymus weight of the males in the high dose (3,000 mg/kg bw/d) gavage group. Thymus weight was not significantly affected by sucralose when administered to rats by gavage at either 1,500 or 750 mg/kg bw/d; nor was it affected in the sucralose-fed group or the diet restricted group. No morphological changes in thymus or any other lymphoid tissues were observed in any of the sucralose treated groups.

In the mid-dose (1,500 mg/kg bw/d) sucralose-gavaged male rats, there appeared to be a trend toward decreasing white blood cell and lymphocyte counts with increasing dose levels of sucralose, but the trend did not reach statistical significance. No significant differences were seen in other immunologic parameters in the sucralose gavage groups relative to the control gavage group. However, because of the large variation seen in the data from the gavaged animals at the mid-dose, the agency finds that the study is inconclusive regarding treatment-related effects for these parameters at the mid-dose.

The agency concludes that the highest dose (3,000 mg/kg bw/d) tested in the gavage groups showed an effect based on the significant changes in thymus weight. Because of the difficulty in interpreting data from the mid-dose animals, the agency has determined that the low dose, 750 mg/kg bw/d, is the no-observed-effect level for the immunological endpoints examined in this study (Ref. 37).

c. *Neurotoxicity testing in mice and monkeys (E008 and E009).* The chlorinated monosaccharide, 6-chloro-6-deoxy-D-glucose (6–CG), is known to be neurotoxic to laboratory animals (Refs. 38 and 39). Because sucralose is a chlorinated disaccharide, McNeil conducted two neurotoxicity studies, one in mice (E008) and one in monkeys (E009). The positive control in these studies, 6–CG, produced strong clinical signs of neurotoxicity, as well as severe morphological changes in the tissues of the central nervous system (CNS). Animals receiving sucralose or an equimolar mixture of sucralose hydrolysis products at doses up to 1,000 mg/kg bw/d did not exhibit any clinical signs of neurotoxicity or morphological changes in CNS tissues (Refs. 5 and 40). The agency concludes that the lack of neurotoxic effects by both sucralose and its hydrolysis products at the tested dose levels in these studies provides assurance that sucralose used as a food additive under the proposed conditions of use will not produce neurotoxic effects.

d. *Diabetic studies in humans (EI56, E157, E168, E170, E171).* In an effort to provide an assessment of any potential effect sucralose use would have on the diabetic population, the petitioner performed a series of clinical studies on diabetic patients. The results obtained from those studies are discussed in this section of this document.

A single-dose cross-over study (E156) was performed in 13 insulin-dependent (IDDM or Type I diabetics) and 13 non-insulin dependent (NIDDM or Type II diabetics) patients to evaluate the effects of a single dose of sucralose (1,000 mg) on short-term glucose homeostasis. Fasting plasma glucose area under the curve (AUC) and fasting serum C-peptide AUC were measured after the consumption of a standardized liquid breakfast meal. This study showed that neither plasma glucose nor serum C-peptide levels were affected by this single dose administration of sucralose in these patients. From this study the agency concludes that sucralose does not adversely affect short-term glycemic control in persons with diabetes mellitus (Ref. 41).

A 6-month clinical study (E157) was performed investigating the effect of sucralose (667 mg/d through oral administration) on glucose homeostasis in patients with NIDDM (Type II diabetes). The study was divided into a screening phase, a testing phase, and a followup phase. Forty-one patients participated in the testing phase of the study. The 41 patients were divided into two groups: 20 patients whose diabetes was managed by insulin and 21 managed by oral hypoglycemic agents (OHA's). Each of these two groups were further subdivided into a sucralose group and a placebo group. Percent concentration of glycosylated hemoglobin (HbA1c) was the primary measure of long-term glycemic control in this study. In addition, the following parameters of glucose homeostasis were measured: (1) Fasting levels of plasma glucose, serum C-peptide, and serum insulin; and (2) postprandial measures of plasma glucose, serum C-peptide, and serum insulin. These parameters were measured after 0, 1, 3, and 6 months of treatment with either sucralose or a placebo (cellulose).

The results from this study showed a small but statistically significant increase in the glycosylation of hemoglobin (HbA1c) from baseline levels in the sucralose-treated group compared to that seen in the placebo group (dataset 1: mean difference of 0.007 percent, $p = 0.005$; dataset 2: mean difference of 0.006 percent, $p = 0.012$) (Ref. 42). This HbA1c effect was observed in the sucralose-treated group at 1 month of treatment and did not significantly increase to higher levels throughout the remainder of the study (mean difference range of 0.006 to 0.008 percent, $p \leq 0.0043$). Overall, during the test phase of the study, no statistically significant changes from baseline were observed in any of the secondary measurements of glucose homeostasis (ie., plasma glucose and serum C-peptide and insulin concentrations). Because of the small patient group sizes in this study, the ultimate clinical significance of the observed HbA1c effect could not be determined (Ref. 42). However, generally speaking, increases in glycosylation in hemoglobin imply lessening of control of diabetes. Thus, the petitioner performed studies E168 and E170 in an attempt to provide an explanation for the observed HbA1c effect.

In study E168 McNeil performed a series of tests to determine whether the increased HbA1c levels observed in study E157 were an artifact of measurement (e.g. interferences related to methodology) or a direct effect of sucralose on the rate of hemoglobin glycation. These tests included a reanalysis of blood samples from study E157 for glycohemoglobin levels; an investigation of the procedures used to measure glycated hemoglobin; and an analysis of the effects of sucralose on glycation of hemoglobin in hemolysates versus intact erythrocytes. Results from these tests confirmed that in E157, HbA1c levels were increased in the sucralose-treated diabetic patients and showed that sucralose had no direct effect on the rate of hemoglobin glycation.

In study E170, red cell preparations from the blood of diabetic and non-diabetic patients were treated with

sucralose (100 mg per liter) to investigate the rate of formation of glycated hemoglobin in the blood. The results of this study showed that sucralose did not affect the rate of formation of glycated hemoglobin (Ref. 42). Thus, there was no evidence that a physicochemical or other influence by sucralose might explain the increased glycation of hemoglobin.

Because studies E168 and E170 did not provide an explanation for the HbA1c effect observed in study E157, study E171 was performed as a repeat study of E157 with a better experimental design, in that E171 had larger patient group sizes and stronger statistical power (90 percent versus 80 percent in study E157) to detect an effect by sucralose on hemoglobin glycation. The 3-month duration for study E171 was deemed adequate because the increased HbA1c levels that were seen at one month of treatment in study E157 did not increase any further at any of the later time points tested in the study. In study E171, 136 NIDDM patients were divided into two groups based on their diabetic therapy (64 taking insulin and 72 on OHA's). Each of these two groups were subdivided equally into a sucralose and placebo group. The study was divided into a screening phase, a testing phase, and a followup phase. Glycosylated hemoglobin (HbA1c) was the primary measure of glucose homeostasis; in addition, the secondary parameters, fasting plasma glucose and serum C-peptide, were measured. Serum insulin levels were not measured in this study.

Results from study E171 showed no statistically significant changes from baseline in the HbA1c levels or any of the other measured parameters of glucose homeostasis in the sucralose-treated groups relative to the placebo control group. The agency concludes from the results of this study that sucralose (667 mg/d) has no effect on long-term glucose homeostasis (as measured by HbA1c) in patients with NIDDM (Refs. 43 and 44). The agency further concludes that the small but statistically significant decline in glycemic control that was observed in the sucralose-treated groups in study E157 was not a clinically significant effect because this effect was not duplicated in a repeat study (study E171) that had a greater statistical power (Ref. 43).

Therefore, based upon the clinical studies of sucralose, FDA concludes that sucralose does not adversely affect glucose homeostasis in patients with diabetes mellitus.

C. Acceptable Daily Intake Estimates for Sucralose

Based on a comprehensive review of the sucralose data base, the agency has selected the rat as the most appropriate experimental model to establish a safe level of sucralose for human ingestion. This selection was based on the following considerations:

(1) The pharmacokinetics data show that the sucralose metabolite profile in rats was qualitatively comparable to that in humans.

(2) In the combined chronic toxicity/carcinogenicity rat study (E057) with sucralose, the animals were exposed in utero, which maximizes the toxicological testing sensitivity.

(3) The combined chronic toxicity/carcinogenicity rat studies (E057) and the carcinogenicity study in rats (E053) were designed to test the toxic potential of sucralose and its hydrolysis products for a duration approximating the lifespan of the species. The agency historically uses life-time studies for safety evaluation of this type of food additive. Such testing effectively allows for the assessment of chronic toxicity including the carcinogenic potential of sucralose.

(4) The majority of the sucralose toxicological data base consists of rat studies, thereby allowing a more comprehensive safety evaluation of sucralose in that species. For these reasons, the agency concludes that the combined chronic toxicity/carcinogenicity study (E057) in rats, interpreted in light of the no-observed-effect level established in other studies (El60, E161, and E162), provides the most appropriate basis for establishing the ADI for sucralose (Refs. 4 and 10). Data in study E057 showed that sucralose was not carcinogenic to rats at concentrations up to 3 percent (1,500 mg/kg bw/d). No toxicologically significant changes in hematology, clinical chemistry, organ weights, or urinalysis were observed in the sucralose-treated rats in this study. Macroscopic and microscopic examinations of the tissues from these sucralose-treated rats revealed no significant treatment-related toxicological effects.

The only treatment-related effect seen in the sucralose-fed rats of this study was decreased body weight gain at the 3-percent dose level. The relationship of this effect to treatment at the 3-percent dose level was corroborated by the diet restriction study (El60). In the diet restriction study (El60), the 1-percent dose level (equivalent to 500 mg/kg bw/d dose in study E057) was established as the no-observed-effect level of sucralose for the observed body weight gain decrement effect (Refs. 10 and 34).

Using the no-observed-effect level of 500 mg/kg bw/d and applying a 100-fold safety factor, the agency has determined an ADI of 5 mg/kg bw/d for sucralose. This ADI estimate is well above the 90th-percentile EDI for sucralose of 1.6 mg/kg bw/d (Refs. 10 and 45).

The agency concludes that the 2-year rat carcinogenicity study (E053) on the sucralose hydrolysis products established a no-observed-effect level at the 0.6 percent dose level (equivalent to 30 mg/kg bw/d). Therefore, the agency has no safety concerns about the sucralose hydrolysis products at their anticipated levels of intake (0.0048 mg/kg bw/d) because of the substantial margin of safety between these levels and the no-observed-effect level.

III. Comments

The agency received several comments on McNeil's sucralose petition. Several comments supported amending the food additive regulations for the safe use of sucralose (Ref. 47). Other comments, principally from Malkin Solicitors (Malkin, formerly Malkin-Janners) and the Center for Science in the Public Interest (CSPI) (Refs. 48 and 49) raised several issues which they claimed McNeil's petition had not addressed. The issues raised by the comments and the agency's responses are discussed in this section of this document.

In addition, CSPI submitted a draft report from Life Science Research Limited of Suffolk, England entitled ''An investigation of diet spillage among rats fed diet containing sucralose.'' This draft report was provided to CSPI by an individual who stated that the study was undertaken by McNeil but was uncertain that the study report had been submitted to FDA. The diet spillage study in rats (El54) was subsequently submitted to the agency by McNeil in March, 1992. As discussed in section II.B.5.a.i. of this document, the agency concludes that the study raises no unique issue and contributes very little to the resolution of the issue of decreased food intake by sucralose-treated rats.

A. Determination of No-Observed-Effect Level and ADI

1. No-Observed-Effect Level in the Chronic Toxicity Study

Malkin pointed to decreases in body weight gain of 13 to 20 percent, 19 to 24 percent, and 20 to 26 percent observed in animals in the three treatment groups compared to control animals in the combined chronic/

carcinogenicity study in rats (E057) and claimed that, because decreases in body weight of greater than 10 percent can be interpreted as an indication of toxicity, a no-observed-effect level was not established in this study. Malkin cited several observations from studies in the McNeil petition that suggest that the decreased body weight gain was not due solely to poor palatability as McNeil asserted.

In addition, Malkin contended that the petitioner overstated the actual doses in the combined chronic toxicity/carcinogenicity study (E057) in rats because the diets were formulated with a constant percentage of sucralose throughout the study. Thus, the actual dose per body weight was variable depending on food consumption and the weight of the animal. Therefore, the dosage received later in life is lower than that received by the young, and Malkin contended that depending on which dosage was used, the no-observed-effect level and the ADI can vary significantly.

FDA agrees in part with certain assertions made in the Malkin comment but disagrees with the overall significance of the findings identified by Malkin. Specifically, as discussed previously, the agency also found that the data in the original petition were not adequate to determine whether the body weight gain decrement was due solely to a palatability-induced decrease in food consumption or whether the weight gain decrement was due to effects mediated by sucralose. Therefore, the petitioner conducted an additional, carefully controlled weight gain study (diet restriction study, E160, which was submitted after the Malkin comment was received) to resolve the body weight gain decrement issue. Based on this study, the agency concludes that sucralose has a treatment-related effect on body weight gain when fed orally to rats at a concentration of 3 percent (Refs. 10, 28, 33, 34, and 46). Also the agency agrees with the comment that the decrements in body weight gain observed in the combined chronic carcinogenicity study (E057) cannot be explained solely by differences in food intake due to reduced palatability of the sucralose-containing diet. The mechanism by which sucralose affects body weight gain in rats is unknown. The agency concludes, however, that a no-observed-effect level for sucralose, as discussed previously, was demonstrated in the diet restriction study (EI60).

Regarding the dosage calculations, the agency considers it inappropriate to limit the dosage calculation to any one time point in the study (Ref. 46). The agency normalizes the data and in doing so takes into consideration the increased dosage during the growing phase and the lower dosage during adulthood to provide an average intake. In reviewing the achieved dosages provided in study E057, the agency found that male rats achieved an average high dose of 1.3 g/kg bw/d, while females achieved an average high dose of 1.7 g/kg bw/d. The average of the two equals 1.5 g/kg bw/d. Thus, the agency concludes that this dose was calculated using the standard techniques for calculating a lifetime dose and is not an overstatement of the actual dose.

2. No-Observed-Effect Level in Developmental Toxicology Studies

Malkin stated that the ''Two-Generation Reproduction Study of Sucralose in Rats'' (E056) did not establish a no-observed-effect level because of dose-related reductions in pup body weight and statistically significant, dose-related decreases in body weight gain in pups from day 1 through weaning in two generations (F_1 and F_2). In addition, Malkin stated that there was a recurring dose-related increase in relative kidney weights.

The purpose of this reproduction study (E056) was to assess the potential effects of sucralose on reproduction. The experimental design of such studies limits the measuring of food consumption by the pups, especially during lactation (Refs. 10, 40, and 50). However, precise food consumption measurements are essential to evaluate the potential for a substance to affect body weight gain. Therefore, study E056 cannot be used to draw conclusions about body weight gain. Moreover, body weight gain effects were comprehensively studied in other studies (El60 and E161). As discussed previously, FDA disagrees with this comment. Regarding the increased kidney weights, microscopic examination of the kidneys of rats in the subchronic studies (El5l and E161) revealed no histopathological changes and therefore, FDA determined that these increases in relative kidney weight in these rats were not toxicologically significant.

Malkin also asserted that the no-observed-effect level in the teratology study in rabbits (El34) is 350 mg/kg bw/d rather than 700 mg/kg bw/d proposed by the petitioner.

Although no frank terata were observed at any of the tested doses in this study (El34), the agency finds that toxicity elicited at the high dose (700 mg/kg bw/d) prevented the use of this dose to assess teratological effects. Therefore, as discussed previously, the agency agrees that the no-observed-effect level in the rabbit teratology study is 350 mg/kg bw/d (Refs. 40 and 50).

3. Derivation of ADI

CSPI challenged the derivation of the ADI for sucralose (15 mg/kg bw/d) conducted by the Food and Agriculture Organization/World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives (JECFA) and by McNeil. CSPI contended that the appropriate ADI ranges from 0.2 to 8 mg/kg bw/d depending on the study used to derive the ADI. CSPI used a large number of safety factors ranging from 10 to 1,000 to derive the ADI from each of the studies which included: (1) The 8-week dose range-finding study (E031); (2) the two-generation reproduction toxicity study (E056); and (3) the long-term feeding studies in the rat (2 years) (E057), the mouse (2 years) (E055), and the dog (1 year) (E051). In addition, CSPI cited the clinical study (E047) as supporting the animal-derived ADI's.

As discussed in section II.C of this document, FDA has evaluated all the studies in McNeil's petition and has concluded that the combined chronic toxicity/carcinogenicity study in rats (E057), interpreted in light of the data in the diet restriction study (El60) and the 26-week gavage study (El6l), provides the most appropriate basis for establishing the ADI for sucralose. This study (E057) provides a no-observed-effect level of 500 mg/kg bw/d; these results are corroborated by data from the diet restriction study (El60) in rat. Applying a 100-fold safety factor (21 CFR 170.22) results in an ADI for sucralose of 5 mg/kg bw/d (Ref. 10).

The combined chronic toxicity/carcinogenicity rat study (E057) provides certain distinct advantages over other studies in the sucralose petition in terms of establishing an ADI. The agency did not use the 8-week range-finding (E031) or two generation reproduction (E056) studies because they were too brief and, compared to chronic studies, they lack the capability to measure general toxicity. The 1-year chronic toxicity study in dogs (E051) showed no toxic effect at any dose tested and thus, provides no basis for concluding that the ADI should be lower than that established in the rat study. Although the 2-year carcinogenicity study in mice (E055) established a higher no-observed-effect level of 1,500 mg/kg bw/d, it did not include an in utero exposure of the animals to sucralose. Finally, the agency notes that the purpose of the clinical study (EO47) was to assess tolerance and acceptance of sucralose and, thus, it was not designed nor intended to

assess the toxicity of this compound (Refs. 10 and 51). Thus, use of the combined toxicity/carcinogenicity study in rats (E057) to establish the ADI for sucralose is sound and scientifically preferred.

B. Immunotoxic Potential of Sucralose

The Malkin comments claimed that the following observations may have significance relative to the potential immunotoxicity of sucralose: (1) Dose-related decreases in thymus weights with concurrent decreases in white blood cell or lymphocyte counts (lymphocytopenia) in the 1-year chronic toxicity study in dogs (E051); (2) dose-related decreases in thymus weight that were seen in the parental rats and offspring in the two-generation reproduction study (E056); and (3) decreased spleen weights at the two highest dosages in the 4- to 13-week sucralose oral gavage rat study (El5l). Malkin further asserted that these findings are important in view of published data that establish that the immune system is a target organ for some chlorinated compounds. Malkin also contended that these alleged immunotoxic effects cannot be explained by decreased food consumption and that a more direct evaluation of immunotoxicity potential should be done for sucralose (Ref. 48).

CSPI also questioned whether sucralose has a toxic effect on the thymus. In their comment, CSPI discussed various effects that were demonstrated in the 4- to 8-week range-finding study in rats (E031), i.e., splenic hypoplasia of lymphoid tissues, cortical hypoplasia of the thymus, and decreased spleen, adrenal, and thymus weights. CSPI also cited the lymphocytopenia that was observed in rodents and dogs in the sucralose studies (Ref. 49).

From a comparative analysis of thymus weight data, body weight data, and food consumption data in the sucralose rat studies, CSPI concluded that the relative thymus weight in sucralose-fed rats is much more severely affected than in diet restricted animals (Ref. 48). CSPI further asserted that thymus histopathology was not evaluated in all of the sucralose studies. CSPI also questioned the appropriateness of the reevaluation of the thymic histopathological examinations by McNeil in the 4- to 8-week range-finding study (E031). Finally, CSPI asserted that adequate studies of immune system function, including a clinical study, should be conducted (Ref. 49).

After the Malkin and CSPI comments were received by FDA, McNeil conducted a 28-day oral immunotoxicity study in rats (EI62) in which a number of immunological parameters were examined. In this study, sucralose was administered by gavage at dose levels of 750, 1,500, and 3,000 mg/kg bw/d and also in the diet at a level of 3,000 mg/kg bw/d. As discussed in section IIB.5 of this document, the only treatment-related effect observed in this study was decreased thymus weight. FDA determined that a dose level of 750 mg/kg bw/d was the no-observed-effect level for this study (Ref. 37). This no-observed-effect level is 1.5 times higher than the no-observed-effect level established from body weight gain decrements observed in studies E057 and E160, which studies FDA used to determine an ADI of 5 mg/kg bw/d for sucralose. The ADI assures that the proposed use levels of sucralose pose no safety concerns regarding immunotoxicity.

In addition, other studies of sucralose lacked evidence of immunotoxic effects. In the combined chronic toxicity/carcinogenicity rat study (E057), a dose of 500 mg/kg bw/d demonstrated no immunodeficiencies in rats exposed in utero, during lactation, and through their entire lifespan. Likewise, no immunotoxic effects were demonstrated in any of the clinical chemistry parameters nor were immunotoxic effects observed in the histopathological examinations of the sucralose-gavaged rats in the 26-week gavage study (EI61), in which sucralose was administered at doses up to 3000 mg/kg bw/d. This study is discussed in section II.B.5.a.ii of this document.

Therefore, the agency concludes that the available animal data provide adequate evidence that sucralose will not be immunotoxic to humans at the projected level of dietary exposure (Refs. 40 and 50).

C. Mutagenicity of 1,6–DCF

Malkin claimed that data in the sucralose petition showed that 1,6–DCF, a sucralose hydrolysis product, is mutagenic in the Ames assay and is a more potent mutagen than unhydrolyzed sucralose in the mouse lymphoma assay. Further, Malkin stated that the mutagenic potential of 1,6–DCF is established by its ability to alkylate 4-(paranitrobenzene)-pyridine in an assay which has been used to demonstrate the alkylating nature of carcinogenic hydrocarbons, some of which were known to bind covalently to DNA, and by the association of 1,6–DCF with DNA in all tissues including the testes. Thus, Malkin asserted that it is imperative to demonstrate in vivo that 1,6–DCF does not covalently bind to DNA or other chromosomal proteins in germ cells (Ref. 48). CSPI also asserted that the DNA-binding capacity and mutagenic potential of 1,6–DCF should be carefully reviewed (Ref. 49).

As discussed in section II.B.2 of this document, the data from the genotoxic studies are of limited toxicological significance because the results of the mutagenic testing were equivocal and because such tests are used primarily as a guide to assess the need for more powerful bioassays. While 1,6–DCF was weakly mutagenic in the Ames test (E020) and the L5178Y TK+/assay (E022, E024), the results from the combined chronic toxicity/carcinogenicity study (E057) and the carcinogenicity study on an equimolar mixture 4–CG and 1,6–DCF (E053) establish that sucralose and its hydrolysis products do not elicit tumor formation. Because of the longer exposure duration and greater testing sensitivity of carcinogenicity bioassays, such as E057 and E053, the negative results in these carcinogenicity bioassays of sucralose and its hydrolysis products (E057 and E053) supersede the equivocal results obtained in the genotoxicity studies on sucralose and its hydrolysis products cited by the Malkin and the CSPI comment (Refs. 5 and 50).

D. Renal Effects

CSPI asserted that McNeil's hypothesized etiology of sucralose-induced rat renal changes (i.e., secondary to cecal enlargement and not likely to be significant at low intake) should be proved and that the renal changes observed in the female rats should be interpreted as being of toxicological significance. Also, the comment asserted that the available data are insufficient to conclude that the nephrocalcinosis (deposition of calcium in the kidney) is only an indirect consequence of cecal enlargement (Ref. 49).

First, nephrocalcinosis is not uncommon in the rat, particularly the female rat (Refs. 21, 22, and 23). Investigators have reported the incidence of renal calcification as high as 100 percent in female rats used as controls with a complete absence of this condition in male rats fed the identical diet (Ref. 21). Because mice and other rodent models do not experience the condition, FDA believes that the rat, especially the female rat, is uniquely sensitive to the development of nephrocalcinosis and, therefore, is an inappropriate surrogate for man with respect to this pathologic endpoint.

Second, as discussed in section II.B.4.a.i of this document, the agency

recognizes that a number of poorly or slowly absorbed compounds mediate changes in physiologic function that result in renal mineralization, as observed in this study (Refs. 6, 21, and 26). In response to the feeding of poorly absorbed compounds, like sucralose, cecal enlargement in association with renal changes occurs frequently in old rats (Refs. 21 and 26). Increased calcium absorption and excretion, pelvic nephrocalcinosis, increased water retention, and alterations of the gut microflora occur as physiologic adaptive responses to changes in osmolality in the gut that lead to cecal enlargement (Refs. 21, 22, and 23). Therefore, cecal enlargement is a physiologic adaptive change rather than a toxic effect (Ref. 26).

Third, in the carcinogenicity study of sucralose hydrolysis products (EO53), which was concurrently conducted in the same laboratory with study E057, the incidence of nephrocalcinosis in the control group was 33 percent (Ref. 26). This incidence is comparable to that observed in the mid- (32 percent) and high- (30 percent) dose treated groups in the combined chronic toxicity/carcinogenicity sucralose study (EO57). The agency concludes that the nephrocalcinosis is not toxicologically significant for the foregoing reasons.

E. Fetal Edema

Malkin stated that the teratology study of sucralose in rats (E030) indicates an apparent increase in the incidence of subcutaneous edema in fetuses. Malkin noted that the expected occurrence of fetal edema at the Life Science Research Limited (LSRL) laboratory of Essex, England, where the McNeil teratology study was conducted, was 12 percent. In contrast, Malkin asserted that the historical incidences of subcutaneous fetal edema for Charles River CD rats is approximately 0.03 percent and the incidence based on data derived from nine United States teratology laboratories is 0.007 percent. Malkin concluded that the unusually large background incidence of edema seen at LSRL may mask a treatment-related increase in subcutaneous edema (Ref. 48).

The agency believes that the most appropriate historical control values to use in considering the significance of a response in an animal bioassay are those pertaining to the identical strain of animal used in the study and drawn from the testing laboratory used for the study (Refs. 40 and 50). It is inappropriate to compare data from Charles Rivers CD rats that were bred in two different countries because, due to genetic divergence, different ranges of normalcy as well as spontaneous malformations are likely to exist for each colony (Ref. 50).

The rat teratology study in question (E030) was conducted in an LSRL laboratory, utilizing a Charles River rat derived in England. The historical control data from LSRL showed the incidence of subcutaneous fetal edema in Charles River rats to range from 0 to 32 percent. In the teratology study in rats (E030), which was performed in England, the reported incidences of subcutaneous fetal edema were 15.6, 20.9, 20.5, and 25.6 percent for the control, low, mid, and high dosages, respectively. These incidences fall within the LSRL historical control range (Ref. 40). Additionally, the slightly increased incidences in subcutaneous fetal edema in the sucralose treated rats raised by the Malkin comment (E030) were not statistically different when compared to their concurrent controls (Refs. 13, 40, and 50). Thus, the incidences of subcutaneous fetal edema identified by the Malkin comment are considered by FDA to be of no toxicological significance.

F. Bioaccumulation

The Malkin comment raised three issues concerning the possible bioaccumulation of sucralose. First, Malkin disputed McNeil's calculation of an ''effective half-life'' of 13 hours for sucralose. Instead, Malkin asserted that sucralose has a ''terminal half-life'' of 24 hours in healthy humans, which is, Malkin asserts, indicative of the potential for sucralose to accumulate in the body of consumers. Further, Malkin stated that the remaining 4 to 7 percent of radioactivity not excreted 5 days after a single dose of sucralose in humans indicates that sucralose may never be totally excreted from the body, even for periodic users. Second, Malkin pointed to data on sucralose metabolism in dogs (EI23) which show that 20 percent of the oral dose was not recovered 4 days after dosing with ^{36}Cl labeled sucralose and claimed that this residual radioactivity represents either potential bioaccumulation, extensive in vivo dechlorination, or both. Finally, Malkin stated that there was a potential for sucralose to accumulate in the fetus because of its extremely slow elimination from fetal tissue.

The available pharmacokinetics data in the petition do not allow the agency to draw definitive conclusions regarding bioaccumulation of sucralose and its metabolites. However, the available evidence on the physicochemical properties of sucralose, such as low lipid solubility and high water solubility, is not representative of compounds that manifest a high potential for bioaccumulation (Refs. 50 and 53). In addition, sucralose is relatively poorly absorbed from the gut in humans in that only 11 to 27 percent of the administered dose is absorbed. Finally, there is little or no evidence of direct tissue toxicity from sucralose in the mouse, rat, and dog, even when administered at high doses for 1 to 2 years. In a practical sense, the absence of tissue toxicity is more important because even if sucralose had accumulated to some limited degree in these animals, no organ toxicity was demonstrated in any of the long-term studies (E055, E057, and E051).

G. Antifertility Effects

Malkin asserted that antifertility effects were observed with unidentified degradation products of sucralose (Ref. 48). In evidence of this assertion, Malkin pointed to results of a study (E004) conducted by McNeil in which sucralose and/or its metabolites distribute to and have a long residual time in testes. Malkin cited a literature publication by Ford and Waites (Ref. 17) where sucralose was shown to inhibit the oxidation of glucose and decrease the concentration of adenosine triphosphate in epididymal spermatozoa. Malkin further asserted that these observations must be reviewed in the context of the known antifertility effects of other chlorosugars (Ref. 48).

The results obtained in study E004 were discounted by the petitioner because there were indications that the sucralose sample used in the study were degraded. A subsequent repeat test (study E107) that was performed by McNeil showed sucralose had no effect on the glycolytic activity of sperm from male rats.

The agency concludes from stability data contained in the sucralose petition that sucralose is stable under the proposed conditions of use (Refs. 52 and 53). Therefore, the agency would not expect significant amounts of degradation products to be formed from the proposed uses of sucralose.

The agency has previously discussed in this preamble the studies mentioned in the Malkin's comment. With regard to the Malkin comment claiming accumulation of sucralose and its metabolites in testes, the available pharmacokinetics data in the sucralose petition do not allow the agency to draw definitive conclusions regarding the bioaccumulation of sucralose and its metabolites. However, neither of the two-generation reproduction studies (E052 and E056) showed any reproductive toxicity that was

treatment-related. Again, this absence of reproductive toxicity is directly relevant to the Malkin comment about antifertility effects and demonstrates that any speculation about bioaccumulation is of no practical significance.

The agency noted insufficiencies in the antifertility studies on sucralose and its hydrolysis products, specifically in their duration, and therefore concludes that they are inadequate to assess the antifertility potential of sucralose (Refs. 5, 18, and 54). More importantly, however, results from the two-generation reproduction studies (E052 and E056) do adequately address any potential toxicological concern regarding the antifertility potential of sucralose and its hydrolysis products. Evidence presented in the reproduction studies supports the conclusion that sucralose and its degradation products do not possess antifertility properties (Refs. 5, 12, and 18).

H. Neurotoxicity Effects

Malkin stated that neurotoxic effects of some chlorosugars have been reported and pointed out that 6-chloro-6-deoxyglucose (6–CG) is used as a positive control for CNS neuropathology and neuromuscular deficits (Ref. 48). Therefore, Malkin stated that neurobehavioural studies of sucralose should be assessed in an appropriate study.

FDA has evaluated the petitioner's neurotoxicity studies, E008 (mice) and E009 (monkey), which compared the potential neurotoxic effects of sucralose or its hydrolysis products with the positive control 6–CG (Refs. 38 and 39). As discussed in section II.B.5.c of this document, FDA finds that neither mice nor monkeys showed neurological effects after receiving sucralose or equimolar mixtures of sucralose hydrolysis products at levels as high as 1000 mg/kg bw/d for 21 and 28 days respectively.

I. Exposure to Sucralose Hydrolysis Products

Malkin stated that in acidic drinks such as powdered cherry drinks (storage temperature, 35 °C) and carbonated soft drinks (storage temperature, 22 °C), sucralose concentrations decrease by 4 percent to 20 percent after a 6-month storage and if, as the petitioner states, the disappearance of sucralose results in the appearance of stoichiometric amounts of the hydrolysis products 4–CG and 1,6–DCF, human exposure to these hydrolysis products will be significantly greater than the 10 mg/kg body weight claimed by the petitioner (Ref. 48).

The agency notes that even if the decomposition noted after 6 months at 35 °C (an 18 percent decrease of sucralose) was accepted as representative of actual use, the probable exposure to hydrolysis products would not change appreciably from the current estimate of 285 µg/p/d (90th percentile, 4.8 µg/kg bw/d) because beverages account for only 13 percent of the estimated exposure to sucralose. Nonetheless, the agency does not believe that such abusive storage conditions should be assumed when considering chronic exposure (Refs. 52 and 53). The data for storage at 20 °C, and for storage at 35 °C for up to 3 months show no decomposition of sucralose within experimental error. The sucralose content of carbonated beverages also does not change significantly under typical storage conditions. Finally, the no-observed-effect level established for the hydrolysis products is 30,000 µg/kg bw/d, so there is an adequate safety margin to allow for additional decomposition of sucralose to the hydrolysis products.

J. The Need for Studies in Special Populations

CSPI stated that, although McNeil showed that sucralose does not affect insulin secretion and action, and glucose metabolism in normal human subjects (E046), non-diabetic rats, and non-diabetic dogs, there are no clinical studies of type I and II diabetics or the ''diabetic'' rat. CSPI contended that sucralose will be in heavy use by diabetics and that before approving sucralose, the agency should require the results of testing of the effects of sucralose in diabetics (Ref. 49).

First, FDA believes that these comments do not preclude the conclusion that the proposed uses of sucralose are safe. The EDI (discussed in section II.A of this document) of sucralose (90th percentile) established by the agency would include those levels expected to be ingested by diabetics (Refs.1, 2, 53, and 55). The 90th percentile level of consumption used by FDA is an amount equivalent to the sweetness that would be provided by the total amount of sugars commonly added to the diet. Thus, the estimates of heavy consumption of sucralose used by FDA would cover estimated intake of sucralose by diabetics who might preferentially select sucralose-containing products.

Second, after this comment was received by FDA, McNeil did perform studies on sucralose in diabetic individuals. Specifically, McNeil has submitted a series of studies (E156, E157, E168, E170, and E171) that investigated the short-term and long-term effects of sucralose on glucose homeostasis in patients with IDDM and NIDDM. These studies were previously discussed in detail earlier in this document. Based upon the data from these studies, the agency concludes that sucralose has no adverse health effects on short-term or long-term glucose homeostasis or any other adverse effect in diabetic patients (Refs. 41, 43, 44, 45). The sucralose exposure tested in the diabetic study E171, where no effect on glycemic control in diabetics was observed, is seven times higher than the 90th percentile EDI estimate expected from the proposed uses of sucralose. This 90th percentile exposure estimate represents the expected use of sucralose by the heavy eater population and also encompasses the level that is expected to be ingested by the diabetic population (Ref. 5).

Additionally, none of the data in the animal studies in the sucralose data base that examined the effect of sucralose on carbohydrate/glucose metabolism provided any evidence to suggest that diabetics would be at any greater risk than the general human population (Ref. 46). These studies show that: (1) Sucralose has no influence on insulin secretion by rats or humans; (2) sucralose has no effect on postprandial or fasting blood glucose levels in animals or humans; (3) sucralose causes no changes in intestinal absorption of glucose or fructose; (4) sucralose has no effect on glucose utilization or on any of the key enzymes modulating glucose metabolism or storage; (5) administration of sucralose results in no clinical or pathological symptoms similar to those observed in diabetes mellitus; and (6) because sucralose has no influence on insulin's action on blood glucose levels, it would not be anticipated to result in difficulties with insulin-based management of diabetes. Therefore, on the basis of the data in the clinical studies and other available information in the sucralose database, the agency has no safety concerns regarding the use of sucralose by diabetic individuals.

Another comment by Malkin speculated that the chlorinated galactose component of sucralose may have an effect on individuals with diminished ability to metabolize galactose (galactosemic individuals). Malkin further speculated that 4-chlorogalactose, a sucralose degradation product, may act as a substrate for enzymes that metabolize galactose in normal individuals, or may inhibit galactosyltransferase, an enzyme largely

responsible for the production of milk in humans.

As discussed previously, from the review of the stability data submitted in the sucralose petition, the agency would not expect significant amounts of degradation products to be formed as a result of the proposed uses of sucralose. Therefore, exposure to degradation products from the use of sucralose would be minimal and would be of no toxicological significance.

In another comment, Malkin criticized the petitioner's metabolism data because the data were obtained from healthy adults and did not address metabolism or safety in children, diabetics, or the obese.

First, as noted, the petitioner did conduct several studies of sucralose use in diabetics. Moreover, there are no data that would suggest any particular reason to expect an increased potential for adverse effects in children and obese people and other subpopulations. The Malkin comment did not present any data or evidence that suggest that these subpopulations are at special risk. In the absence of such data, the agency determines an additive's safety based on studies conducted in healthy test animals at doses far in excess of the maximum anticipated exposure in humans. In addition, in setting an ADI, the agency uses a 100-fold safety factor after determining the highest no-adverse-effect level. The agency uses a 100-fold safety factor as a means to account for differences between animals and humans and to account for differences in sensitivity among humans. For these reasons, the agency believes that studies aimed at addressing effects in the subpopulations indicated are not warranted.

K. Labeling

In response to a November 22, 1991 (56 FR 58910), request by FDA for comments on a proposed monograph for sucralose for inclusion in the Food Chemicals Codex, Malkin stated that the name sucralose is inaccurate, deceptive, and will mislead consumers because of the close similarity to the name sucrose, a product for which sucralose might be a replacement. Because sucralose is a chlorinated version of a disaccharide, Malkin contended that the common name should not misrepresent the makeup of the material. Malkin cited § 102.5(a) and (c) (21 CFR 102.5(a) and (c)) and contended that the common name should indicate that the material is a disaccharide, reflect the presence of chlorine, and avoid confusion with sucrose. Malkin stated that the name used by the FAO/WHO JEFCA ''trichlorogalactosucrose'' or a similarly accurate name such as trichlorofructogalactose should be used.

Section 403(i)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(i)(2)) deems a food that is fabricated from two or more ingredients to be misbranded unless its label bears the common or usual name for each ingredient. Section 102.5(a) states, in part, that: ''The common or usual name of a food, which may be a coined term, shall accurately identify or describe, in as simple and direct terms as possible, the basic nature of the food or its characterizing properties or ingredients. The name shall be uniform among all identical or similar products and may not be confusingly similar to the name of any other food that is not reasonably encompassed within the same name.'' Section 102.5(c) addresses the need for the common or usual name of a food to include a statement of the presence or absence of any characterizing ingredients or components, whether such ingredients need to be added, whether the absence or presence has a bearing on price, and similar issues that may cause a consumer to purchase a product that is not what it appears to be.

Sucralose is a single ingredient and has no other characterizing ingredients or components that are added or removed. Thus, § 102.5(c) does not govern the question of what is the appropriate name for this additive.

Under § 102.5(a), a substance may be described by a coined term provided that it accurately identifies, in as simple and direct terms as possible, the nature of the food, i.e., the food additive sucralose. While the names suggested by Malkin may be suitable for describing the nature of the substance to a chemist, they are not the most direct and simple terms for the average consumer. FDA recognizes that the precise chemical names of additives may not be helpful for consumers and has permitted the use of a simple coined name that consumers can understand. For example, none of the three intense sweeteners currently allowed in food, saccharin, aspartame, and acesulfame potassium, are described by their specific chemical names. This causes no confusion, however. The important issue is whether the name is commonly used for the substance and whether that name could be misleading for some reason.

Although Malkin states that the name trichlorogalactosucrose is used by JEFCA for this additive, that organization has since the comment was submitted accepted sucralose as the preferred name. Additionally, the additive is regulated under the name sucralose in both Canada and Australia. Thus, it is consistent with the international marketplace, including other English speaking countries, to describe the additive by the name sucralose. Similarly, the Food Chemicals Codex has also published a monograph under the name sucralose. For these reasons, the agency concludes that the name sucralose is the common name, accurately identifies the additive, and will not mislead consumers.

IV. Conclusion

The agency has evaluated all the data in the petition and other information and concludes that the proposed uses of sucralose are safe. Therefore the agency concludes that the food additive regulations should be amended as set forth in this document.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

V. Environmental Effects

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum, from DiNovi, Chemistry Review Branch, to Anderson, Novel Ingredients Branch, September 21, 1993.

2. Memorandum, from DiNovi, Food and Color Additives Review Section, to Anderson, Direct Additives Branch, May 18, 1989.

3. Memorandum from Roth, HFS–506, to Review Staff Office of Premarket Approval, October 26, 1994.

4. Memorandum, from Roth, HFS–506, to Anderson, Division of Product Policy, October 26, 1994.

5. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, August 8, 1990.
6. Addendum memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, April 12, 1991.
7. Memorandum, from Griffiths, Additives Evaluation Branch, to Anderson, Direct Additives Branch, August 22, 1988.
8. Addendum memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, August 12, 1991.
9. Memorandum, from Dunkel, Genetic Toxicology Branch, to McLaughlin, Direct Additives Branch, May 23, 1984.
10. Memorandum, from Whiteside, Additives Evaluation Branch No. 2, to Anderson, Novel Ingredients Branch, May 26, 1995.
11. Memorandum, from Whiteside, Additives Evaluation Branch No. 2., to Anderson, Direct Additives Branch, January 21,1994.
12. Memorandum, from Collins, Mammalian Reproduction and Teratology Team, to Gryder, Additives Evaluation Branch, August 15, 1987.
13. Memorandum, from Welsh, Whole Animal Toxicology Branch, to McLaughlin, Direct Additives Branch, February 1, 1984.
14. Addendum Memorandum, from Whiteside, Additives Evaluation Branch, to Anderson, Direct Additives Branch, November 12, 1991.
15. Memorandum, from Collins, Mammalian Reproduction and Teratology Team, to Gryder, Additives Evaluation Branch, October 2, 1987.
16. Memorandum, from Welsh, Mammalian Reproduction and Teratology Team, to Bleiberg, Division of Toxicology, July 15, 1986.
17. Ford, W. C. L., and G. M. H. Waites, ''A Reversible Contraceptive Action of Some 6-chloro-6-deoxy Sugars in the Male Rat,'' *Journal of Reproduction and Fertility*, 52:153–157, 1978.
18. Memorandum, from Whitby, Additives Evaluation Branch, to Anderson, Direct Additives Branch, December 20, 1988.
19. Memorandum, Cancer Assessment Committee, October 20, 1987, January 26, April 6, and July 13, 1989.
20. Memorandum, from Dua, Division of Pathology, to Lin, Additives Evaluation Branch, February 11, 1992.
21. Lord, G. H., and P. M. Newberne, ''Renal Mineralization—A Ubiquitous Lesion in Chronic Rat Studies,'' *Food Chemistry and Toxicology*, 28:449–455, 1990.
22. Newberne, P. M, M. W. Conner, and P. Estes, ''The Influence of Food Additives and Related Materials on Lower Bowel Structure and Function,'' *Toxicologic Pathology*, 16:184–197, 1988.
23. Vaughan, O. W., and L. J. Filer, ''The Enhancing Action of Certain Carbohydrates on the Intestinal Absorption of Calcium in the Rat,'' *Journal of Nutrition*, 71:10–14, 1960.
24. United Nations (UN) Environmental Programme, International Labour Organization, World Health Organization, Food and Agriculture Organization of the U.N., ''Principles for the Safety Assessment of Food Additives and Contaminants in Food,'' Geneva: World Health Organization, 1987 (Environmental Health Criteria, 70), pp. 41-42.
25. De Groot, A. P., and V. J. Feron, ''Effects of Very High Dietary Levels of Lactose on the Kidneys of Rats.'' In: Report R4812 Central Institute for Nutrition and Food Research (CIVO/TNO). Zeist, the Netherlands: CIVO/TNO; October 1975/ March 1976: 1-6.
26. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, April 1, 1991.
27. Memorandum, from Sucralose Working Group, to Rulis, Novel Ingredients Branch, August 3, 1992.
28. Memorandum, from Sucralose Working Group, to Pauli, Novel Ingredients Branch, December 21, 1992.
29. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, May 11, 1987.
30. Memorandum, from Bleiberg, Additives Evaluation Branch, to Anderson, Direct Additives Branch, October 20, 1987.
31. Memorandum, from Graham, Additives Evaluation Branch, to Direct Additives Branch, August 3, 1987.
32. Submission to FAP 7A3987, McNeil Specialty Products, May 5, 1992.
33. Memorandum, from Barton, Experimental Design and Evaluation Branch, to Anderson, Novel Ingredients Branch, April 26, 1994.
34. Memorandum, from Whiteside, Additives Evaluation Branch No. 2, to Anderson, Novel Ingredients Branch, June 29, 1994.
35. Memorandum, from Whiteside, Additives Evaluation Branch No. 2, to Anderson, Novel Ingredients Branch, July 8, 1994.
36. Memorandum, from Barton, Experimental Design and Evaluation Branch, to Anderson, Novel Ingredients Branch, March 18, 1994.
37. Memorandum, from Hinton, Biochemical and Analytical Branch, to Anderson, Novel Ingredients Branch, March 7, 1995.
38. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, February 17, 1988.
39. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, April 12, 1988.
40. Addendum Memorandum, from Whiteside, Additives Evaluation Branch No. 2, to Anderson, Novel Ingredients Branch, May 26, 1995.
41. Memorandum, from Wilcox, Epidemiology Branch, to Anderson, Novel Ingredients Branch, October 7, 1994.
42. Memorandum, from Whiteside, Scientific Support Branch, to Anderson, Novel Ingredients Branch, November 13, 1997.
43. Memorandum, from Fleming, Center for Drug Evaluation and Research, to Anderson, Novel Ingredients Branch, August 21, 1997.
44. Memorandum, from Barton, Division of Mathematics, to Anderson, August 28, 1997.
45. Addendum Memorandum, from Whiteside, Scientific Support Branch, to Anderson, Novel Ingredients Branch, November 13, 1997.
46. Memorandum, from Yetley/Einhorn, Clinical Nutrition Branch, to Anderson, Director Additives Branch, January 8, 1990.
47. Comments, from supporters of the petition, to Dockets Management Branch.
48. Comments, from Malkin Solicitors.
49. Comments, from Center for Science in the Public Interest (CSPI).
50. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, December 13, 1990.
51. Memorandum, from Whiteside, Additives Evaluation Branch, to Anderson, Direct Additives Branch, November, 12, 1991.
52. Memorandum, from DiNovi, Food and Color Additives Review Section, to Anderson, Direct Additives Branch, December 6, 1990.
53. Memorandum, from Modderman, Food and Color Additives Review Section, to Anderson, Direct Additives Branch, May 20, 1988.
54. Memorandum, from Graham, Additives Evaluation Branch, to Anderson, Direct Additives Branch, December 27, 1988.
55. Memorandum, from Glinsmann, Clinical Nutrition, to Anderson, June 18, 1991.

VII. Objections

Any person who will be adversely affected by this regulation may at any time on or before May 4, 1998, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 172

Food additives, Incorporation by reference, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

2. Section 172.831 is added to subpart I to read as follows:

§ 172.831 Sucralose.

The food additive sucralose may be safely used as a sweetening agent in foods in accordance with current good manufacturing practice in an amount not to exceed that reasonably required to accomplish the intended technical effect in foods for which standards of identity established under section 401 of the Federal Food, Drug, and Cosmetic Act do not preclude such use under the following conditions:

(a) Sucralose is the chemical 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside (CAS Reg. No. 56038–13–2).

(b) The additive meets the specifications of the ''Food Chemical Codex,'' 4th ed. (1996), pp. 398–400, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the the Division of Product Policy (HFS–206), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204–0001, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC 20204–0001, or the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(c) The additive may be used as a sweetener in the following foods:

(1) Baked goods and baking mixes;
(2) Beverages and beverage bases;
(3) Chewing gum;
(4) Coffee and tea;
(5) Dairy product analogs;
(6) Fats and oils (salad dressing);
(7) Frozen dairy desserts;
(8) Fruit and water ices;
(9) Gelatins, puddings, and fillings;
(10) Jams and jellies;
(11) Milk products;
(12) Processed fruits and fruit juices;
(13) Sugar substitutes (for table use);
(14) Sweet sauces, toppings, and syrups;
(15) Confections and frostings.

(d) If the food containing the additive purports to be or is represented to be for special dietary use, it shall be labeled in compliance with part 105 of this chapter.

Dated: March 30, 1998.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

[FR Doc. 98–8750 Filed 4–1–98; 8:45 am]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[DE–12–1–5886; FRL–5990–2]

Approval and Promulgation of Air Quality Implementation Plans; Delaware New Source Review

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is conditionally approving a State Implementation Plan (SIP) revision submitted by the State of Delaware for the New Source Review (NSR) program. This revision establishes and requires the review and permitting of new major sources and major modifications of major sources in nonattainment areas. The changes primarily pertain to the ozone precursors, volatile organic compounds (VOCs) and nitrogen oxides (NO_x). EPA is conditionally approving the NSR SIP revisions submitted by Delaware because the revisions strengthen the SIP, but Delaware failed to revise the NSR regulations to adopt all of the provisions relating to modifications in serious and severe ozone nonattainment areas, required by the 1990 Clean Air Act Amendments. In addition Delaware must make additional revisions to satisfy conditions related to emission offsets and public participation as required by federal regulations. Delaware has submitted a written commitment to satisfy the conditions of this final rule and to revise the SIP within one year of this rulemaking.

EFFECTIVE DATE: This final rule is effective on May 4, 1998.

ADDRESSES: Copies of the documents relevant to this action are available for public inspection during normal business hours at the Air Protection Division, U.S. Environmental Protection Agency, Region III, 841 Chestnut Building, Philadelphia, Pennsylvania 19107; the Air and Radiation Docket and Information Center, U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460; and Delaware Department of Natural Resources & Environmental Control, 89 Kings Highway, P.O. Box 1401, Dover, Delaware 19903.

FOR FURTHER INFORMATION CONTACT: Linda Miller, (215) 566–2068.

SUPPLEMENTARY INFORMATION:

I. Background

On January 12, 1998 (63 F.R. 1804), EPA published a notice of proposed rulemaking (NPR) for the State of Delaware. The NPR proposed conditional approval of Delaware New Source Review requirements, Delaware Regulation 25, Sections 1 and 2.

The formal SIP Revision was submitted on January 11, 1993. The State has committed by letter dated February 10, 1998 to amend the SIP to correct the following deficiencies within one year of publication of this rulemaking by adding the following:

1. The special rule for modifications of sources in serious and severe ozone nonattainment areas, consistent with Sections 182(c)(7) and (8) of the Clean Air Act.

2. Public participation procedures consistent with 40 CFR 51.161. Regulation No. 25 does not specify the public participation procedures to be used in issuing nonattainment NSR permits.

3. A requirement that where the emissions limit under the SIP allows greater emissions than the potential to emit of the source, emission offset credit will be allowed only for control below this potential as found in 40 CFR 51.165(a)(3)(ii)(A).

4. Provisions for granting emission offset credit for fuel switching, consistent with 40 CFR 51.165(a)(3)(ii)(B).

5. Requirements consistent with 40 CFR 51.165(a)(3)(ii)(C)(1) for the crediting of emission reductions achieved by shutting down an existing source or curtailing production or operating hours below baseline levels (shutdown credits). These requirements must include a provision that such reductions may be credited if they are permanent, quantifiable and federally-enforceable, and if the area has an EPA-approved attainment plan.

6. A requirement that the shutdown or curtailment is creditable only if it occurred after the date of the most recent emissions inventory or attainment demonstration consistent with 40 CFR 51.165(a)(3)(ii)(C)(1).

7. A requirement that all emission reductions claimed as offset credit shall be federally enforceable consistent with 40 CFR 51.165(a)(3)(ii)(E).