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ORIGINAL SUBMISSION

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GRN # 000006

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July 20, 1998

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HAND-DELIVERED

Laura M. Tarantino, Ph.D.
Acting Director
Office of Premarket Approval
Center for Food Safety and
Applied Nutrition
Food and Drug Administration
1110 Vermont Avenue, N.W.
Washington, D.C. 20036

1998 JUL 21 P 2:20

Re: Cytec Industries, Inc. — GRAS Notification for Dioctyl Sodium Sulfosuccinate; Our File No. CY04825/05

Dear Dr. Tarantino:

On behalf of our client, Cytec Industries Inc., we are hereby submitting, in triplicate, a generally recognized as safe (GRAS) Notification, in accordance with proposed 21 C.F.R. § 170.36 ("Notice of a claim for exemption based on a GRAS determination"), 62 *Fed. Reg.* 18938, 18960 (April 17, 1997), for the use of dioctyl sodium sulfosuccinate (DSS) as a wetting agent or solubilizer for flavor emulsion stabilizers in carbonated and non-carbonated soft drinks. DSS would be used at a level equivalent to up to 10 parts per million of the finished beverage.

Although DSS has long been used in both the food and pharmaceutical industry, this GRAS Notification is based on scientific procedures and methods. The potential exposure to DSS from this use is well within both the Food and Drug Administration's (FDA) and FAO/WHO Joint Expert Committee on Food Additives (JECFA) acceptable daily intakes for this material. As the enclosed JECFA monograph demonstrates, there is widely available published literature demonstrating the safety of the substance at the intake levels possible from this use. The data Cytec has relied upon in reaching this determination has previously been submitted to the Agency, and is therefore available for the Agency's review in this instance.

98S-0103

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We trust you will find the enclosed Notification acceptable. Should any questions arise during the review process, please do not hesitate to contact us, preferably by telephone, so that we may respond as quickly as possible.

Very truly yours,

Ralph A. Simmons

Enclosures

ORIGINAL

Before the
FOOD AND DRUG ADMINISTRATION
Department of Health and Human Services
Washington, D.C.

GRAS NOTIFICATION

Name of Notifier:	Cytec Industries, Inc.
Post Office Address:	All communications on this matter are to be sent in care of Counsel for the Notifier, Ralph A. Simmons, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001. Telephone: (202) 434-4120.
Name of Substance and Intended Use:	Dioctyl sodium sulfosuccinate [CAS Reg. No. 577-11-7] for use as a wetting agent or solubilizer for flavor emulsion stabilizers used in the production of carbonated and noncarbonated soft drinks.
Dated:	July 20, 1998

Ralph A. Simmons
Counsel for Cytec Industries, Inc.

1. Claim of GRAS Status

(i) Name and Address of Notifier:

Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, New Jersey 07424

All communications on this matter are to be sent in care of Counsel for the Notifier, Ralph A. Simmons, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001. Telephone: (202) 434-4120.

(ii) Common or usual name of the notified substance:

Dioctyl sodium sulfosuccinate, or DSS

(iii) Applicable conditions of use:

As a wetting agent or solubilizer for flavor emulsion stabilizers used in the production of carbonated and noncarbonated soft drinks, for addition at levels equivalent to up to 10 parts per million (ppm) of the finished beverage as consumed.

(iv) Basis for GRAS determination

The described use of DSS has been shown to be generally recognized as safe (GRAS) through scientific procedures, as discussed more fully in the accompanying summary of the basis for the GRAS determination.

(v) Statement of availability of data

The data and information that are the basis for the GRAS determination are available for the Food and Drug Administration's review and copying or will be sent to FDA upon request.

Indeed, the Notifier believes that copies of all the relevant toxicological data are in the Agency's files.

* * *

The foregoing and attached information considered, it is respectfully submitted that the use of dioctyl sodium sulfosuccinate as a wetting agent or solubilizer for flavor emulsion stabilizers used in the production of carbonated and noncarbonated soft drinks, for addition at levels equivalent to up to 10 parts per million of the finished beverage in the form in which it is consumed, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because it is generally recognized as safe.

Respectfully submitted,

CYTEC INDUSTRIES, INC.

By
Ralph A. Simmons
Keller and Heckman LLP

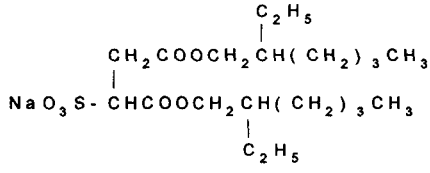
COUNSEL FOR THE NOTIFIER

2. Identity of the Notified Substance

Chemical Name: Dioctyl sodium sulfosuccinate; or, bis(2-ethylhexyl) sodium sulfosuccinate

CAS Registry No.: 577-11-7

Molecular and Structural Formulas: $C_{20}H_{37}O_7SNa$



Quantitative Composition: Complies with purity specifications set forth below.

Method of Manufacture: Produced by reaction of 2-ethylhexyl alcohol with maleic anhydride followed by addition of sodium bisulfite.

Characteristic properties: DSS is an anionic surface-active agent. It is a waxy white solid, soluble in many organic solvents. It dissolves slowly in water. DSS is stable in acid and neutral solutions, and hydrolyzes in alkaline solutions.

Food-Grade Specifications: DSS complies with the specifications set forth in the Food Chemicals Codex, 3d Ed. (1981), pp. 102-104. These include the following:

Assay	Not less than 98.5% $C_{20}H_{37}O_7SNa$, calculated on the dried basis.
Arsenic (as As)	Not more than 3 ppm
Bis(2-ethylhexyl)maleate	Not more than 0.4%
Clarity of solution	Passes test
Heavy metals (as Pb)	Not more than 10 ppm
Loss on drying	Not more than 2%
Residue on Ignition	Between 15.5% and 16.2%

3. Information on Self-Limiting Levels of Use:

In the applications described herein, DSS will be used in carbonated and noncarbonated soft drink beverages at levels that will not exceed 10 parts per million in the finished beverage. This is identical to the maximum level at which DSS is listed at 21 C.F.R. § 172.810 as a wetting agent in fumaric acid-acidulated dry beverage bases and fruit juice drinks. The 10 ppm maximum concentration is a well-established effective level for DSS in beverage products. The Notifier has not conducted testing to determine a level that would be self-limiting in the notified application.

4. Summary of Basis for GRAS Determination

A. Data and information relied on to establish safety

As indicated above, general recognition of safety in this instance is based on scientific procedures, in keeping with 21 C.F.R. § 170.30(b). As discussed more fully below, a large volume of toxicological data on DSS is available; these data have previously been reviewed by the Food and Drug Administration and an acceptable daily intake determined that is far in excess of that resulting from the notified use. The data have also been evaluated by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA), which also has published an acceptable daily intake that comfortably exceeds the intake calculated below. Consideration of cumulative intake from the currently cleared uses plus the notified use further confirms the safety of the additional use.

Toxicity of DSS and Acceptable Daily Intake

DSS is a surface-active agent that fulfills several unique, niche requirements in the food and pharmaceutical areas. The substance has been used in drug products since 1943. Its primary use in this area is in laxative preparations and fecal softeners. DSS has been used in food products since 1965. Due to its long-term use in these specific markets, numerous investigations have been conducted to determine the toxicological effects of extended exposure to ingested DSS. These data have been previously evaluated by both the Food and Drug Administration and by the Joint FAO/WHO Expert Committee on Food Additives. As part of its safety evaluation process, JECFA published a toxicological monograph on DSS. (*See* WHO Food Additives Series: 28, Toxicological evaluation of certain food additives and contaminants. Prepared by the 37th Meeting of the Joint FAO/WHO Expert Committee on Food Additives; World Health Organization, Geneva 1991.) A copy of the toxicological monograph appears as Appendix A to this notification.

A brief summary of the most relevant studies on DSS follows. In short-term testing, rats fed DSS for 4 weeks had no significant effects at dose levels up to 1%. Feeding DSS to rats for nine weeks at a 25% dietary concentration resulted in a decline in growth rate; the investigators suggested this was due to poor palatability, as food consumption was also decreased. DSS dosage at 2% and higher in the feed for 16 weeks also led to growth retardation, with virtually complete mortality at 4% or 8% in the feed. In a 24-week study, no adverse effects were observed when DSS was administered at levels up to 0.87 g/kg in the feed. Rats fed DSS for 26 weeks at levels up to 1.5% had no significant effects on weight gain and no adverse effects on

hematology, urinalysis, organ weights, or in organ histology. Thus, the 1.5% level appears to be the no-observed effect level (NOEL) for subchronic intake of DSS.

In chronic testing, rats receiving 1.0% DSS in the feed for two years had reduced body weight gain but no pathological changes upon gross and microscopic examination. A dose of 0.5% DSS in the feed was a NOEL in this study. Finally, in a one-year feeding study in dogs, a daily dose of 30 mg/kg did not result in any treatment-related signs of toxicity. No adverse effects were found upon gross and microscopic examination of G.I. tract organs and tissues, and serum enzyme analysis indicated no chronic liver toxicity.

It should be noted that both FDA and JECFA toxicological evaluators previously had concerns with regard to the potential for DSS to elicit adverse reproductive or teratological effects. This possibility has been extensively examined in several studies, most notably in a multigeneration reproduction study that was conducted at the request of a Scientific Review Panel convened by FDA in 1984 with the purpose of evaluating the safety of DSS for pharmaceutical and food uses. Upon review of the full report of the three-generation study, the FDA evaluators concurred with the investigators' conclusions that the no-observable effect level for DSS, when administered in the diets of rats for three successive generations, is 0.1% for body weight loss of parental animals and offspring, with a NOEL for reproductive parameters of 1.0%. The FDA toxicologists also concluded that reduced pup survivability observed in some litters at the 1.0% dose level was a spurious finding that was not directly related to treatment with DSS. Thus, in this study as well as the others summarized above, the NOEL for DSS administration,

0.1% in the diet, was based solely on a reduction in body weights for parental animals and pups.[1/] The conclusions reached by JECFA in the appended monograph are substantively identical to FDA's.

The studies discussed above, and several others addressed in the JECFA monograph, are summarized in Table 1 below. Complete references are given in the monograph set forth in Appendix A.

Table 1
Subchronic and Chronic Feeding Studies on DSS

Study	Spp	Duration	Route	NOEL	Effects	Pathology
Guerrant, 1937	Rat	9 wk	diet		Single dose (25%), b.w. ↓	
Benaglia, 1943 a	Rat	24 wk	diet	>0.87g/kg		Yes
Fitzhugh & Nelson, 1948 b	Rat	16 wk	diet	<2%	b.w.↓	
Hazelton, 1958	Rat	28 day	diet	>1%	single dose	
Taylor, 1966	Rat	26 wk	diet	>1.5%		Yes
Fitzhugh & Nelson, 1948 b	Rat	2 yr	diet	0.5%	b.w.↓ at 1%	Yes
Benaglia, 1943 a	Rbt	24 wk	IG	>0.124g/kg	single dose	Yes
Case, 1977	Dog	1 yr	gav	>30 mg/kg	single dose	Yes
Benaglia, 1943 a	GP	15 mos	water	>1g/L	single dose	
Amer. Cyanamid, 1970	Rat	repro	diet	lact:<0.5% terato>1%	pup b.w.↓ due to palatability	

1/ *See* FDA Memoranda, dated September 12, 1986, and May 19, 1987, from Charles V. Frazier, Team Leader, Standards and Monitoring Branch, to Lawrence Lin, Ph.D., Direct Additives Branch. For the Agency's ready reference, copies of both memoranda appear as Appendix B to this notification.

Hoechst Roussel, 1976 c	Rat	terato	diet	terato: 1%	maternal b.w.↓ at 2%	
Hoechst Roussel, 1979 c	Rat	terato	diet		single dose	
MacKenzie, 1990	Rat	repro	diet	tox: 0.1% repro: >1%	b.w.↓ at 0.5 and 1%	

Notes: Spp = Species; Rbt = Rabbit; GP = guinea pig; repro = reproductive toxicity study, terato = teratology study (under "Duration" heading); IG = intragastric; gav = gavage; water = drinking water; NOEL = no-observed effect level; lact = lactation effect; terato = teratological effect, repro = reproductive effect (under "NOEL" heading); b.w.↓ = decline in body weight gain; Pathology = Pathology conducted on primary organs.

It is apparent from the foregoing that the "effect" on the basis of which the no-observed effect levels for the various studies were established is the observation of a decline in body weight growth only. Other effects associated with changes in organ weight or histopathological observations were not found.

The acceptable daily intake (ADI) for DSS is determined by applying a suitable safety factor to the NOEL established in the feeding studies. Generally, when long-term testing has been conducted, a 100-fold safety factor is applied to the NOEL from the chronic toxicity studies. In the case at hand, the NOEL for chronic intake of DSS in the diet is 0.5%; this would support an ADI of 0.005% (50 ppm). Although the NOEL established in the multigeneration study, 0.1% in the feed, is somewhat lower than the chronic value, use of the higher NOEL would be reasonable here since the two-year study reflects the results of chronic intake over the lifetime of the test animals while the multigeneration study is designed to study the effect of DSS at a limited phase of life in which the animals are most vulnerable.

This fact notwithstanding, both the FDA and JECFA evaluators chose to rely on the NOEL from the reproductive toxicity study to set their respective ADIs. This was due to the general practice of employing the lowest available ADI, and also to the fact that the multigeneration study reflects more current toxicity testing standards than the older chronic feeding study.

The NOEL from the multigeneration reproductive study, 0.1% in the diet, is equivalent to an ingestion level of 50-150 mg/kgbw/day. In keeping with its usual practice for studies of this duration, FDA established its ADI by applying a 100-fold safety factor to the NOEL, thus calculating an ADI of 0.5 mg/kgbw/day. In its determination, because of the lack of a recent chronic study, JECFA applied a more conservative safety factor of 500, to reach an ADI of up to 0.1 mg/kgbw/day for DSS. (*See* WHO Technical Report Series 859, Evaluation of certain food additives and contaminants. Forty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives; World Health Organization, Geneva.) Based on the standard individual body weight of 60 kg, FDA's ADI for DSS is equivalent to intake of 30 mg/person/day; the JECFA ADI equates to intake of 6 mg/person/day.

Intake of DSS From Notified Use

As indicated above, the use of DSS dealt with here is in the preparation of flavor emulsions used in the production of carbonated and noncarbonated soft drinks. These beverages are generally prepared by combining water and carbon dioxide (for the carbonated drinks) with a syrup that contains concentrated flavoring oil, sweeteners, and other ingredients. The syrup must be prepared as a stable emulsion to prevent separation of the flavor oils upon dilution with water.

[redacted]

Thus, emulsion stabilizers are used to prepare the flavor concentrate in a stable form. Use of DSS facilitates this process by functioning as a wetting, or solubilizing agent, for the emulsion stabilizer. In this application, as in other beverage uses, DSS will be employed only at very low levels, with a maximum addition level equivalent to 10 ppm in the finished beverage as consumed.

For the sake of conservatism in calculating the potential intake of DSS resulting from this use, we will assume that it will be employed at the maximum anticipated level of 10 ppm in all soft drinks. Data on individual intake of such beverages is available in the U.S. Department of Agriculture's (USDA) study, "Foods Commonly Eaten by Individuals: Amount per Day and Per Eating Occasion" (March 1982, reviewed and approved for reprinting February 1990). Based on the reporting of food consumed by participants in a three-day survey, the USDA study found that the daily level of consumption of carbonated soft drinks by the 90th percentile consumer of these products is 556 g/person/day (or, about 0.56 kg/person/day).[2/] If DSS is present in these beverages at a concentration of 10 ppm, or 10 milligrams per kilogram, the daily intake of DSS by the 90th percentile consumer will be 5.6 mg/person/day. We note that this value necessarily exaggerates actual intake since it is based on the assumptions that DSS will be used in all soft

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[2/] USDA also recorded consumption data for noncarbonated soft drinks. The survey report states that most of such beverages consumed were prepared from powdered mixes. Beverages prepared from dry mixes are not included in the use for which this notification is submitted; indeed, DSS is currently permitted for this use under 21 C.F.R. § 172.810. Thus, the consumption data for noncarbonated soft drinks are not included here. Considering the inherently conservative nature of the USDA survey for estimating food intake, and since noncarbonated beverages will, at least to some extent, be consumed in place of carbonated beverages, the 90th percentile intake value for carbonated soft drinks is believed to be a reasonable estimate of consumption of the beverages of interest here.

drinks and is always present at the maximum anticipated use level of 10 ppm. In addition, the 3-day survey procedure used by USDA will tend to result in a high estimate of individual food intake over extended periods of time because of the short duration of the survey.

Cumulative Intake of DSS

The sources of intake of DSS fall into two overall categories: food and drugs. Pharmaceutical applications for DSS include laxative formulations, stool softener products, and vitamin/mineral supplements. The primary use is believed to be in stool softeners, which are used only infrequently and, thus, do not represent a source of chronic exposure. Use of DSS in supplements is primarily in high-iron products which likewise are directed towards short-term use, *e.g.*, during pregnancy or to treat anemia. Thus, chronic ingestion of DSS is expected to result almost exclusively from its use in food.

Use of DSS in the food sector has occurred for a sufficiently long period (since 1965) to permit calculation of the actual level of intake resulting from the existing uses. The United States (the National Research Council, on behalf of FDA) sponsors periodic surveys of food additive use, which provide data on the actual quantities of added substances going into food applications. The principal survey for trends in food additive usage is the recording of total poundage for substances used by the food industry; five such surveys have been conducted, in 1970, 1975, 1976, 1982, and 1987. Information on food use of DSS was reported in the last three surveys (see Appendix C). As shown there, the per capita intake for DSS from food uses varied from 0.6 to 2 micrograms per person per day (μg/day).

[redacted]

In 1977, FDA sponsored a more detailed survey of the food industry with regard to specific food uses and levels of addition for substances used in food. While FDA regulations permit use of DSS in a number of foods including drinks and desserts prepared from dry mix, cocoa beverages, and foods containing gums, the survey found it used only in beverages made from dry mixes (see Appendix C). Further, even though the regulation clears DSS for this use at levels of up to 10 mg/kg (ppm), the actual reported DSS use level was only 0.59 mg/kg, far below the cleared level.

The data from the 1977 survey were also combined with information from a survey of food intake to derive additive intakes for high-percentile consumers of the foods that contain the additives. For the reported use of DSS in 1977, the mean age-weighted DSS intake for individuals over two years of age was 56 μg/day; the 90th percentile consumer's intake was 130 μg/day. These intake estimates make use of the exaggerative assumption that DSS is used in *all* beverages consumed and, thus, may be viewed as very conservative estimates of intake from the uses that have been permitted to date.

The long history of practical experience with marketing of DSS in the food industry suggests that the substance will be used in selected "niche" markets in which it excels relative to other emulsifiers. Indeed, 1987 poundage data for all emulsifiers indicate a total market of 58 million pounds, for a per capita intake of 300 mg/day. The 1987 use of DSS in the food supply represents just 1/810,000 of the total emulsifier market (see Appendix C).

The maximum estimated intake level given above for current uses of DSS in food is 130 μg/day, or 0.13 mg/day. Cumulative intake of DSS from all food uses, therefore, will not exceed

the total of this value and the 5.6 mg/day intake conservatively calculated above for soft drink use, or about 5.7 mg/day. This is below the ADI set by JECFA for DSS, and is only a small fraction of the ADI established by FDA.

B. Information unfavorable to the GRAS determination

The Notifier is not aware of any reports of investigations or other information that might appear to be inconsistent with the GRAS determination.

C. Basis for concluding that the notified use of DSS is GRAS

FDA describes the criteria for determining GRAS status for a particular use of a substance through scientific procedures under 21 C.F.R. § 170.30(a) and (b). Section 170.30(a) states that general recognition of safety must be based on the views of experts qualified by scientific training and experience to assess the safety of substances added to food. In the case at hand, two well-qualified bodies of experts, FDA and JECFA, have evaluated the data available on DSS and have established intake levels that the respective experts consider to be safe based on these data. Even based solely on the more conservative conclusions of JECFA, the notified use of DSS is safe by reference to the ADI.

GRAS status must also be based on common knowledge throughout the relevant scientific community that the substance is not harmful under the conditions of intended use. The thorough evaluation of the safety of DSS conducted by JECFA involved the participation of scientific experts from both the United States and the international community, and the results of

the evaluation were published through the usual FAO/WHO mechanism. Clearly, there is wide acceptance in the scientific community knowledgeable about the safety of substances added to food that DSS may be safely used in food at the levels contemplated here.

Section 170.30(b) states that general recognition of safety based on scientific procedures requires the same amount and quality of scientific evidence as that required to obtain clearance as a food additive. In establishing their respective ADIs, FDA and JECFA both relied on well-established scientific standards and procedures for assessing the safety of substances added to food. The level of intake of DSS considered acceptable by both expert bodies, based on full consideration of the quality and quantity of available data, is above the cumulative level of intake of DSS in food as a result of the notified use. Finally, FDA states that GRAS determinations based on scientific procedures shall be based on generally accepted and available data, information, etc., that ordinarily are published but may also be corroborated by unpublished information. Much of the toxicological data have been published in widely disseminated journals. (See full references given in the monograph set forth in Appendix A.) Notably, these include results of the two-year chronic feeding study in rats and one-year feeding study in dogs, and the multigeneration reproduction study in rats. The latter study provided the key data based on which the FDA and JECFA ADIs were established. Moreover, the publication of the JECFA monograph and the basis for establishment of its ADI further disseminated the publicly available data supporting the general recognition of safety of DSS in the application that is the subject of this notification.

* * *

Considering the foregoing, we respectfully submit that all criteria for general recognition of safety based on scientific procedures are met and, thus, that dioctyl sodium sulfosuccinate is generally recognized as safe for use as a wetting agent or solubilizer for flavor emulsion stabilizers used in the production of carbonated and noncarbonated soft drinks at levels equivalent to up to 10 parts per million of the finished beverage.

Appendix A

Pages 000020 - 000034 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Appendix B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date September 12, 1986

From Team Leader, Standards and Monitoring Branch (HFF-156)

Subject Evaluation of A Three-Generation Reproduction Study on Dioctyl Sodium Sulfosuccinate in Rats

To Lawrence Lin, Ph.D.
Direct Additives Branch (HFF-334)

FOOD ADDITIVE PETITION No. 8T-3365

American Cyanamide Co.
Lederle Laboratories Division
Middletown Road
Pearl River, NY

This is an evaluation of the Final Report on a Three-Generation Reproduction Study with Dioctyl Sodium Sulfosuccinate in Rats conducted at Hazelton Laboratories America, Inc. Madison, Wisconsin (Study No. 6123-122) and submitted as part of a petition to Docket Number 78N-036L Docket Management Branch HFA-305. The study was initiated on October 4, 1984 and terminated on December 30, 1985. During the study DSS was administered in the diet to three sucessive generations of male and female rats (30/sex/group) at levels of 0.0, 0.1, 0.5 and 1.0%. The males in the (Fo) parental group were exposed to the diets at least 10 weeks and the females 2 weeks prior to mating to produce the F1 litters. All descendant animals were exposed to the test material in utero, while nursing, continuously from weaning throughout mating, gestation and lactation except for the F3 litters which were sacrificed after weaning and animals from other generations that were culled or not selected for parents of the succeeding generation. Included in the report are summaries and individual data on mean body weight, body weight gain, food consumption and compound consumption for males and females during the premating phases; group mean and individual body weight and food intake data and compound consumption for females during gestation and lactation; male fertility indicies, summary and individual litter data through Day 21 of lactation, and gross pathological observations of all adults and the F3 weanlings.

SUMMARY: 3-Generation Reproduction Study in Rats given DSS in their Diet

Groups of 30 male and 30 female Crl:CD (SD) BR immature rats (Fo parents) purchased from Charles River Laboratories, Portage, Michigan were fed at dietary levels of 0.0%, 0.1%, 0.5% and 1.0% dioctyl sodium sulfosuccinate (DSS). The test article was prepared at a concentration to permit administrations at the above listed dosage levels. Fresh diets were prepared and offered weekly. The control group animals received only the basal diet. Feedings of the compound (product code 24951-01, control Lot Nos. 4DSS002 and 5DSS002), supplied by the sponsor, began with the Fo parents, males 10 weeks and females 2 weeks prior to mating. The Fo_1's were then mated to produce an F_1 litter. The F_1's were exposed to DSS at the same dose levels as their parents at

[redacted]

least 10 weeks post weaning, and the breeding program was repeated to produce F_2 animals. Groups of F_2 animals were fed the same diets for at least 10 weeks post weaning, and the breeding program was repeated to produce F_3 litters. All parental animals were observed twice daily for overt changes in appearance or activity, or any indication of toxicity including death. Moribund animals were sacrificed if they were not expected to survive until the next observation period. Those animals that died on test were subject to a gross necropsy and all tissues were preserved in 10% buffered formalin.

Body weights for males were recorded weekly throughout the study. For females, body weights were recorded weekly during premating phases; on days 0, 7, 14, and 20 of gestation; and days 0, 7, 14, and 21 of lactation. Feed consumptions were recorded weekly during premating phases for both males and females. Feed consumptions of females were measured twice weekly during gestation (day 0-4, 4-7, 10-14, 14-17 and 17-20) and lactation (days 0-4, 4-7, 7-10, 10-14, 14-17 and 17-21).

BREEDING PROGRAM

In each parental generation breeding was initiated by selecting one male and one female at random from animals on the same treatment and placing them in a double size screen-bottom cage. Sibling and half-sibling matings were avoided. Vaginal smears were taken daily, and the presence of a copulatory plug or sperm in the vaginal smear was considered evidence of positive mating. The day on which such evidence was found was considered Day 0 of gestation; the female was then removed and return to a single-sized screen-bottom cage. Each pair had a maximum of 21 days to achieve mating. Females for which no positive mating was observed were placed in a plastic cage after the mating period. Approximately 15 days after the completion of mating, females were placed in individual plastic cages supplied with bedding material, a feed jar, and a water bottle. Females were allowed to deliver and care for their own young with a minimum of distrubance. The first day that an entire litter was observed was considered Day 0 of lactation for that litter. Litters were examined as soon possible after delivery (Day 0 of lactation). Individual pup weight and the number of pups and still borns were recorded. Intact dead pups were examined macroscopically. Four days after birth (Day 4 of lactation) pups were culled from the litters at random to achieve a maximum litter size of 10, with 5 males and 5 females/litter if possible. In addition, when possible, 10 pups/dose group (five/sex) were selected from culled pups in each generation sacrificed, and placed in formalin fixative for possible future evaluation. Pups were weighed individually and examined for external abnormalities on Days 7, 14, and 21 of lactation. In addition the sex of the pups were recorded on Day 21 of lactation. Pups were allowed to nurse for 21 days before weaning. All offsprings were weaned directly onto their parents' diets.

Animals were selected at random from available litters so that each litter was represented. Thirty males and females/treatment groups were continued on their parents' diet. In addition one male and one female F1 pup were selected at random from each weaned litter and designated to be used for a possible recovery phase. Recovery animals were checked

twice daily for mortality and body weights at least once during the holding period. A decision was made by the sponsor not to proceed with an optional recovery study. Therefore, all F1 offspring selected for the recovery phase were sacrificed and discarded and no data on them are presented in this report. Twenty weanlings/sex/group from the F3 litter were selected at random for gross necropsy and tissue preservation. Weanlings not selected for continuation on the reproduction study or for necropsy were subjected to gross external examination, sacrificed, and discarded.

Matings were carried out to produce litters as follows:

Fo (Original parents) $\rightarrow F_{1a}$ litters
F_{1a} (F_1 parents) $\rightarrow F_{2a}$ litters
F_{2a} (F_2 parents) $\rightarrow F_{3a}$ litters

GROSS PATHOLOGY

All Fo, F_1 and F_2 adult animals (including barren males and females) were subject to gross necropsy after their litters had been weaned. Selected tissues and organs and tissues having gross lesions were preserved in 10% buffered formalin.

Reproduction and Pup Survival Indices

The following indices were calculated and reported for all groups in each generation: mating, female fertility, male fertility, gestation viability, weaning and sex ratio (See Table III).

RESULTS

A. General Behavior, Appearance and Survival

1. Parental Rats
There were no treatment-related clinical observations for adult animals during the study. Alopecia was noted with similar frequency in control and treated groups. Malocclusion and/or related signs were observed sporadiocally throughout control and treatment groups. When necessary, the incisors of affected animals were clipped to alleviate the condition. Survival was 100% for all groups of males and females throughout the three generations of this study. No animals died on test and only one animal, an Fo high-dose male, was sacrificed in moribund condition due to a nontreatment-related condition (Animal No. C25201, fractured nasal bones).

2. Pups
There were no treatment-related clinical observations for pups while nursing (lactation period). One female pup in the control group of the F_3 litter was icteric on Day 4. Another control pup from a different litter was missing the left eye. Alopecia, tumors and rough hair coat were recorded on day 21 for three pups (two males and one female) from one F_2 litter at the 0.5% dose level. Pups in the F_1 litter suckled

without any problems. Ineffecient suckling, or no milk observed in the abdomen, of F_2 litter pups on day 4 of lactation was observed as follows:

Control group	-	3 pups from 2 litters
0.1% group	-	7 pups from 5 litters
0.5% group	-	18 pups from 10 litter
1.0% group	-	10 pups from 5 litters

The frequency of this observation in F_3 litters was:

Control group	-	0
0.1% group	-	0
0.5% group	-	1 pup
1.0% group	-	17 pups from 7 litters

The survival of pups in the 1.0% group of F_3 litters was influenced by the ineffective suckling and may account for the disparity in pup survivability on Day 4 of lactation (controls 98.5* and 1.0% group 93.7*). The report addressed the increase in stillborns for the F3 litters' 1.0% group (perinatal pup survival) but did not allude to the continued survival problem with this group of animals at Day 4 (Viability index see Table 56). Other than this isolated incidence of decreased survival in the 1.0% group of the F_3 litters, survival across the three generations was excellent.

*Corrected from data in the report which gives values of: controls, 95.3% and 1.0% group, 91.4%.

B. Parental Body Weights

Body weights at the 1.0% dose level were lower than those of controls during the premating phase for males in all three generations and for F_1 and F_2 females. Body weights of F_1 and F_2 males and females in the 0.5% group were also low during the premating phase. There were no consistent significant differences in body weight gains for either sex during any generation (see Table I and Figure 1).

C. Pup Weights

Initial pup weights (Day 0 of lactation) were significantly lower than those of controls only for the high-dose (1.0% group) during the third generation. Lower pup weight gains in mid and high dose groups were significant at these levels on Day 21 for all three generations (see Table II and Figure 2).

D. Food Consumption

For the most part, food consumption values were comparable between treatment groups and their controls. It decreased during the premating growth phase for both sexes, mostly in males. It remaining low during gestation and then increased appreciablly during lactation (see Table II).

E. Reproduction Data

There were no significant differences from the control for male fertility, female fertility, mating, gestation indices, days required to mate, or the length of gestation. No parental females aborted or had physical or behavioral abnormalities during gestation or lactation across the three generations of the study.

F. Pathology Data

Individual necropsy results for all adults and the F_3 weanlings did not reveal any evidence of adverse macro or microscopic findings attributed to treatment.

G Results of Test Diets and Basal Diet Analyses

Mean concentrations of DSS in the diet for the determination of homogenieity at 0.1% and 1.0% dose levels were 0.0984% and 0.972% respectively. Results of stability determinations indicate that DSS is stable in the diet being stored at ambient conditions for 8 days (90 to 95% of theoretical values and after being frozen from 8 to 28 days (94 to 102%) of theoretical. Cumulative means for periodic analyses were 0.100%, 0.499%, and 0.999% of 0.1%, 0.5% and 1.0% dose levels respectively, and demonstrated that the anticipated levels of DSS were acheived in the test diets.

DISCUSSION

The author concluded that for DSS, when administered in the diets to three sucessive generations of rats, the no-observable effect level (NOEL) for body weight loss of parental animals and offspring was 0.1%, the NOEL for reproductive parameters was 1.0%. We concur with the conclusions but feel that the pup survivability in the 1.0% groups of F_3 litter (stillborn and those alive on Day 4 before culling) even though lower than the control groups, was a spurious finding not directly related to treatment since it was not seen in either the F_1 or F_2 litters at the 1.0% dose level.

CONCLUSION::

DSS administered in the diet to three sucessive generations of rats at levels of 0.5% and 1.0% caused a reduction in body weights for parental males of all generations and for F_1 and F_2 females. In addition, the pup weights of these levels were lower than those of the controls.

There was no evidence of effects on growth or reproductive performance except for the isolated incidence of an increased number of pups born dead (stillbirths) in the F_3 litters of the 1.0% group and some pups with suckling problems. On the basis of the weight changes, the NOEL is the lowest dose administered (0.1%)

Charles V. Frazier

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date May 19, 1987

From Team Leader, Study & Protocol Team
Standards & Monitoring Branch (HFF-156)

Subject Dioctyl Sodium Sulfosuccinate (DSS)

To Lawrence Lin, Ph.D.
Direct Additives Branch (HFF-334)
Through: Associate Director for Toxicological Evaluation (HFF-152)
Samuel I. Shibko, Ph.D SI. 5/20/87

FOOD ADDITIVE PETITION No. 8T-3365

American Cyanamid Co.
Lederle Laboratories Division
Middletown Road
Pearl River, NY

In response to the recommendation of the DSS Scientific Review Panel, a three-generation reproduction study of DSS in the rat was performed under the joint sponsorship of American Cynamid Co., Mead Johnson Co., Plough, Inc. and Stuart Pharmaceuticals. The final report was submitted under cover letter of July 17, 1986 and evaluated by the Division of Toxicology (memo HFF-156 Frazier/Lin dated September 12, 1986).

Dioctyl sodium sulfosuccinate (DSS) is used as a food additive in a variety of foods. DSS (under the name docusate sodium) is also used in small amounts in prescription drug products to ensure dissolution and as a stool softener in over-the-counter products. The wide-spread use of DSS in products regulated by FDA prompted the Agency to conduct a thorough review of all data and information collected to assess the safety of DSS to humans. Questions arose within FDA concerning the reviewed scientific data on DSS and its related potassium (DKS) and calcium (DCS) salts. To resolve these questions, FDA convened a panel of expert scientists from other agencies within the Federal Government.

The Panel, after reviewing the available data, information and views concerning the teratogenicity and reproductive toxicity of DSS and DCS, concluded the following in response to the charter questions (Report of March, 1984):

1. DSS, DCS, and DKS should not be considered as potential human teratogens.

2. Based on the 3-generation reproduction study of DSS in which treatment was continued through lactation and a significant decrease in pup survival was observed during lactation, the panel concluded that the "findings provide grounds for concern which should be explored further."

3. The Panel saw "no compelling reason to alter the accepted 1000 fold safety factor [used for teratogens by FDA] based on the data reviewed."

4. "For the theraputic use of DSS, ... a safety margin of nearly 120 fold is adequate."

5. The data presented "suggest that DSS has the potential to produce adverse reproductive effects in the laboratory animals treated with large doses. .... it appears the human risk is very low."

The Panel therefore recommended conduct of the following studies:

1. "A standard FDA three-generation reproductive study of DSS using rats and mice and including pair-fed as well as untreated controls."

2. "Additional pharmacokinetics and biotransformation studies of DSS to include a determination of the occurrence of DSS and its metabolites in breast milk."

3. "Continued epidemiologic surveillance of pregnancy outcome in women treated with sulfosuccinates (docusates)."

Prior to the formation of the expert panel FDA and industry had been refining a suitable protocol for a 3-generation reproduction study. Subsequent to the panel's report, in a letter to Mark Novitch, MD, Deputy Commissioner of FDA, dated October 2, 1984, Dr. Marvin Friedman, stated that in a September 21, 1984 meeting between industry and FDA members (Dr. Flamm and his staff) all details of the protocol had been worked out to everyone's satisfaction. Dr. Friedman also stated in his letter that the consensus opinion was that this type of study in the mouse is unvalidated. He stated further that at the meeting it was concluded that at the end of the rat study, industry and FDA would meet again to discuss whether a second species was needed and that FDA wanted a determination of blood, milk and pup levels of DSS and its metabolites only if there was a significant effect on reproduction. Dr. Friedman announced that the rat study was scheduled to start October 4, 1984 at Hazelton-Raltech, Madison, Wisconsin.

The FDA memo of the September 21, 1984 conference stated: 1) "The Center's Staff concurred with industry's request to defer the requirement of a reproduction study in mice pending completion and evaluation of the reproduction study in the rat" 2); "it would not be necessary to include pair-fed controls in the reproduction study"; and 3) "the visitors agreed that a pharmacokinetic study might be performed if toxic effects in rat pups during lactation were confirmed."

The reproduction study was completed December 30, 1985, the final report was submitted on July 17, 1986 and evaluated (HFF-156 memo Frazier/Lin dated September 12, 1986). In the evaluation, DT concluded that the no-observable effect level (NOEL) was 0.1% DSS in the diet or 50-150 mg/kg/day, based on a reduction of body weights for parental males of all generations and F_1 and F_2 females. There was no evidence of effects

on reproductive performance except for isolated incidences of poor survival (stillbirths) in the F_3 litters of the 1.0% group and some pups with suckling problems in the F_2 and F_3 litters. The acceptable daily intake (ADI) based on this study, using FDA's safety factor of 100 fold for 3-generation reproduction studies, would be 0.5 mg/kg/day or 25 mg/person/day for a 50 kg human. This ADI is comparable to the tentative ADI of 25 mg/person/day established from a rat teratology study using a NOEL of 500 mg/kg/day and a 1000 fold safety factor. Therefore, the dosage of DSS consumed by humans would pose no reproduction or teratological problems. The question raised by Dr. Ann Wilk/HFN-120 (memo Oct. 20, 1986) concerning pantothenic acid nutriture at high doses of DSS has been addressed and resolved by Dr. Frattali of Division of Nutrition/HFF-160. Dr. Frattali concluded in his memo of March 2, 1987 that "the probability of observing pantothenic acid deficiency in the United States is considered to be extremely low."

In view of the satisfactory outcome of the recently conducted 3-generation rat reproduction study, and in accordance with the concensus opinion at the September 21, 1984 conference, we conclude that the data are adequate to support safety and establishment of an ADI, and that a second study in the mouse and the pharmacokinetic study are not necessary.

The Panel's final recommendation concerned the epidemiologic surveillance being conducted by FDA. The panel recommended that the surveillance be continued. A summary report on the surveillance has not been written.

Conclusion

It is the opinion of Division of Toxicology that the reproductive safety data are adequate to support the food additive uses of DSS. We defer to the Center for Drugs and Biologics for action on the petitioner's request of July 17, 1986 to reopen the Administrative Record on Docket Number 78N-0362 for the purpose of classifying DSS as a Category I ingredient in that docket.

Charles V. Frazier
Team Leader

Appendix C

PB91-127266

1987 Poundage and Technical Effects Update of Substances Added to Food

Committee on Food Additives Survey Data

Food and Nutrition Board

Institute of Medicine

National Academy of Sciences

Washington, D.C., 1989

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

[illegible]	TOTAL POUNDS		9	12	[illegible]	[illegible]	[illegible]
	MATCHED POUNDS						
	1975/82/87	*		3		.2	.2
	1982/87	*				.2	.2

SUBSTANCE		NUMBER OF MATCHED COMPANIES	1970	1975	1976	1982	1987
			YEAR, (TOTAL NUMBER OF COMPANIES) TOTAL AND MATCHED POUNDS REPORTED				
(CONTINUED)							
	TECHNICAL EFFECTS:	F05 .2					
1066 DIOCTYL SODIUM SULFOSUCCINATE							
	TOTAL COMPANIES		*		*	(4)	*
(577-11-7)	TOTAL POUNDS				65	210	71
	MATCHED POUNDS						
	1976/82/87	*			60		
	1982/87	*				120	71
	CFR REFERENCE(S):	172.810					
8760 DICKY ACETOPHENONE							
	TOTAL COMPANIES		*	*		*	*
(29631-86-9)	TOTAL POUNDS		3				
	MATCHED POUNDS						
	1975/82/87	*					
	1982/87	*					
9667 DIPHENYL ETHER							
	TOTAL COMPANIES		*	*	*	*	*
(101-84-8)	TOTAL POUNDS				.4		
	MATCHED POUNDS						
	1976/82/87	*			.4		
	1975/82/87	*					
	1982/87	*					
	CFR REFERENCE(S):	172.515					
2997 1,3-DIPHENYL-2-PROPANONE							
	TOTAL COMPANIES		*	*		(4)	*
(102-04-5)	TOTAL POUNDS		3	4		7	1
	MATCHED POUNDS						
	1975/82/87	*		1		1	1
	1982/87	*				7	1
	TECHNICAL EFFECTS:	F05 1					
	CFR REFERENCE(S):	172.515					

Notes

* means three or fewer reports were received.

Calculation of per capita intakes

		1976	1982	1987
1.	Reported pounds	65	210	71
2.	Adjusted pounds[1/] (Reported pounds ÷ 0.6)	108	350	118
3.	per capita in grams/day (Adjusted pounds ÷ US population for specific year x 454 g/pound ÷ 365 day/year)	0.62 μg	1.87 μg	0.60 μg
4.	per capita, expressed in mg/kg bw (per capita ÷ 60 kg)	0.00001	0.00003	0.00001
5.	per capita as fraction of proposed ADI (0.25 mg/kg bw)	1/25,000	1/8,333	1/25,000

[1/] Because the U.S. survey captures about 60% of US food companies, it is assumed that the reported poundage could represent 60% of an ingredients use and an "adjusted" poundage is calculated as shown. For DSS, because the three survey poundages are approximately the same, the reported poundage is more probably the entire market and the 0.6 adjustment is an over estimation.

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
PB80-113418

Survey of Industry on the Use of Food Additives (1977)

(U.S.) National Research Council, Washington, DC

Prepared for

Food and Drug Administration, Rockville, MD

31 Oct 79

SUB NR: 8072 NAME: DIOCTYL SODIUM SULFOSUCCINATE LISTED: APPENDIX 1 PART A

NR OF REPORTS: USERS * 1978 ANNUAL POUNDAGE: 66.00 YEAR OF FIRST REPORTED USE: 1968
NON-USERS *

TECHNICAL EFFECTS/ FLAVOR TYPES REPORTED	CODE	NAME	NR REPORTS
	27	SURFACE-ACTIVE AGENT	*

USAGE LEVELS:

FOOD CATEGORY	USUAL USE: USE LEVEL (WTD MEAN - %)	USUAL USE: LOSS >25%	USUAL USE: REPORTED AS ADDED/REMAINING	HIGHEST REPORTED USE: USE LEVEL (ABSOLUTE - %)	HIGHEST REPORTED USE: LOSS >25%	HIGHEST REPORTED USE: REPORTED AS ADDED/REMAINING	NUMBER OF RESPONSES IN THIS CATEGORY
23 NON-ALCOHOLIC BVGS				0.000059		ADDED	*
238 DRINK MIX-DRY	0.000059		ADDED				

1295

000050

Appendix A

APPENDIX 2

CLASS 1	CLASS 2	CLASS 3
Foods Sold Ready to Eat, Cook, or Use (Not for Industrial Resale)	Mixes and Concentrates (Not for Industrial Resale)	Industrial Intermediates

MAJOR CATEGORY 22: SNACK FOODS (continued)

Subcategories	Subcategories	Subcategories
A--potato chips and sticks, not fabricated but flavored		
B--potato chips and sticks, plain		
C--popped corn, flavored		
D--popped corn, unflavored		
E--appetizers, multi-component		
F--snack crackers, filled		
G--dietetic products		
Z--other (including cocktail crackers and "Ritz" and "Hi-Ho" types)		

MAJOR CATEGORY 23: BEVERAGES --TYPE I (NON-ALCOHOLIC)

Subcategories	Subcategories	Subcategories
A--beverages, uncarbonated, containing less than 10% of natural juices (see also 08H)	A--mixes	
	B--dry mixes (e.g., "Tang", "Wyler's", etc.)	
C--soft drinks, carbonated, cola-type	C--mixes	
D--soft drinks, carbonated, fruit flavors	D--mixes	
E--soft drinks, carbonated, other (including ginger ale, root beer, etc.)	E--mixes	
F--carbonated water, plain soda		
G--quinine water		
H--high-electrolyte and isotonic drinks (e.g., "Gatoraid")	H--mixes	
I--dietetic products (including low-calorie and sugar-free drinks)	I--mixes	
Z--other [Note: See 24D for cocktail mixes.]		

MAJOR CATEGORY 24: BEVERAGES --TYPE II (ALCOHOLIC)

Subcategories	Subcategories	Subcategories
A--beer, ale, other malt beverages including malt liquor		
B--brandy, whiskey, rum, vodka		
C--gin		
D--premixed cocktails	D--cocktail mixes, dry and liquid	

FREQUENCY DISTRIBUTIONS OF AVERAGE DAILY INTAKE FROM ALL INTENTIONAL ADDITION TO FOODS

AGE GROUP	TOTAL SAMPLE	EATERS NO.	EATERS PCT	EATERS ONLY MEAN**	EATERS ONLY STD-DEV	EATERS ONLY 50-PCTL	EATERS ONLY 90-PCTL	EATERS ONLY 95-PCTL	EATERS ONLY 99-PCTL	TOTAL SAMPLE (EATERS & NONEATERS) MEAN**	TOTAL SAMPLE 50-PCTL	TOTAL SAMPLE 90-PCTL	TOTAL SAMPLE 95-PCTL	TOTAL SAMPLE 99-PCTL
NAS SUBSTANCE 5071 : DIMETHYLPOLYSILOXANE														
SOURCE BY CATEGORY:		08(96%)	14(4%)	04(1%)	19(1%)									
				INTAKE IN MILLIGRAMS							INTAKE IN MILLIGRAMS			
0 - 5 MO.	62	15	24.2%	.10	.16	.041	.43	.56	.56	.025	-	.041	.066	.56
6 - 23 MO.	275	238	86.5%	.45	.65	.25	.96	1.4	3.3	.39	.17	.89	1.4	3.3
2 - 5 YR.	903	903	100.0%	.57	.67	.36	1.4	1.8	3.1	.57	.36	1.4	1.8	3.1
6 - 12 YR.	1,776	1,771	99.7%	.49	.58	.30	1.2	1.5	2.6	.49	.30	1.2	1.5	2.6
13 - 17 YR.	1,133	1,131	99.8%	.47	.58	.26	1.2	1.5	2.8	.47	.26	1.2	1.5	2.8
18 - 44 YR.	3,990	3,967	99.4%	.40	.52	.21	1.0	1.3	2.2	.40	.21	1.0	1.3	2.2
45+ YR.	4,198	4,184	99.7%	.45	.55	.28	1.1	1.3	2.3	.45	.28	1.1	1.3	2.3
2+ YR.	12,000	11,956	99.6%	.45	.56	.26	1.1	1.4	2.5	.45	.25	1.1	1.4	2.4
NAS SUBSTANCE 5072 : DIOCTYL SODIUM SULFOSUCCINATE														
SOURCE BY CATEGORY:		23(100%)												
				INTAKE IN MICROGRAMS							INTAKE IN MICROGRAMS			
0 - 5 MO.	62	2	3.2%	31	27	12	50	50	50	1.0	-	-	-	50
6 - 23 MO.	275	98	35.6%	43	62	28	80	140	500	15	-	45	74	200
2 - 5 YR.	903	481	53.3%	59	69	36	130	180	320	31	9.0	90	130	240
6 - 12 YR.	1,776	868	48.9%	62	62	45	140	180	280	30	-	100	140	240
13 - 17 YR.	1,133	398	35.1%	62	54	40	150	180	220	22	-	81	130	190
18 - 44 YR.	3,990	1,167	29.2%	50	58	35	120	160	290	15	-	47	82	180
45+ YR.	4,198	480	11.4%	48	46	25	120	140	180	5.5	-	12	36	120
2+ YR.	12,000	3,394	28.3%	56	59	35	130	170	260	16	-	54	94	180
NAS SUBSTANCE 5076 : ETHOXYLATED MONO- AND DIGLYCERIDES (POLOXYETHYLENE (20) MONO- AND DIGLYCERIDES OF FATTY ACIDS)														
SOURCE BY CATEGORY:		01(100%)												
				INTAKE IN MILLIGRAMS							INTAKE IN MILLIGRAMS			
0 - 5 MO.	62	5	8.1%	1.4	*	1.4	1.4	1.4	1.4	.11	-	-	1.4	1.4
6 - 23 MO.	275	218	79.3%	21	14	20	39	49	58	17	15	37	44	58
2 - 5 YR.	903	901	99.8%	40	18	40	63	70	85	40	40	63	70	85
6 - 12 YR.	1,776	1,767	99.5%	59	24	57	90	99	120	59	57	90	99	120
13 - 17 YR.	1,133	1,124	99.2%	70	30	68	110	120	150	69	68	110	120	150
18 - 44 YR.	3,990	3,970	99.5%	63	30	62	100	120	140	62	61	100	120	140
45+ YR.	4,198	4,140	98.8%	62	30	62	99	110	140	62	61	99	110	140
2+ YR.	12,000	11,910	99.2%	61	29	59	99	110	140	61	59	98	110	140
NAS SUBSTANCE 5078 : ETHYL CELLULOSE														
SOURCE BY CATEGORY:		03(79%)	01(19%)	10(2%)										
				INTAKE IN MILLIGRAMS							INTAKE IN MILLIGRAMS			
0 - 5 MO.	62	5	8.1%	.018	.012	.011	.037	.037	.037	.0013	-	-	.011	.037
6 - 23 MO.	275	219	79.6%	1.4	7.0	.15	.33	.48	49	1.1	.11	.32	.40	49
2 - 5 YR.	903	900	99.7%	1.3	7.0	.31	.52	.59	29	1.3	.31	.52	.59	29
6 - 12 YR.	1,776	1,766	99.4%	1.3	6.4	.46	.72	.82	41	1.3	.45	.72	.82	41
13 - 17 YR.	1,133	1,126	99.4%	1.8	9.8	.53	.88	1.0	48	1.8	.53	.88	1.0	48
18 - 44 YR.	3,990	3,963	99.3%	2.2	12	.45	.82	.96	58	2.2	.45	.82	.96	58
45+ YR.	4,198	4,125	98.3%	2.5	15	.40	.75	.90	54	2.5	.39	.75	.90	54
2+ YR.	12,000	11,880	99.0%	2.1	12	.43	.78	.92	53	2.0	.43	.77	.92	53

(**) NOTE: GREAT CAUTION MUST BE EXERCISED TO ENSURE THAT [illegible] INTRODUCTORY TEXT).

------NAS SUBSTANCES------
5071 5072 5076 5078

BEST ORIGINAL COPY

19677

000052

FREQUENCY DISTRIBUTIONS OF AVERAGE DAILY INTAKE FROM ALL INTENTIONAL ADDITION TO FOODS

AGE GROUP	TOTAL SAMPLE	EATERS NO.	EATERS PCT	EATERS ONLY MEAN**	EATERS ONLY STD-DEV	EATERS ONLY 50-PCTL	EATERS ONLY 90-PCTL	EATERS ONLY 95-PCTL	EATERS ONLY 99-PCTL	TOTAL SAMPLE (EATERS & NONEATERS) MEAN**	TOTAL SAMPLE 50-PCTL	TOTAL SAMPLE 90-PCTL	TOTAL SAMPLE 95-PCTL	TOTAL SAMPLE 99-PCTL
NAS SUBSTANCE 5071 : DIMETHYLPOLYSILOXANE														
SOURCE BY CATEGORY:		08(97%)	14(2%)	01(1%)	19(1%)									
				INTAKE IN MICROGRAMS PER KILOGRAM						INTAKE IN MICROGRAMS PER KILOGRAM				
0 - 5 MO.	62	15	24.2%	15	24	7.5	63	82	82	3.7	-	7.7	11	82
6 - 23 MO.	275	238	86.5%	42	61	20	94	130	350	37	17	88	110	350
2 - 5 YR.	903	903	100.0%	36	44	22	89	120	170	36	22	89	120	170
6 - 12 YR.	1,776	1,771	99.7%	17	21	9.5	43	56	100	17	9.4	42	56	100
13 - 17 YR.	1,133	1,131	99.8%	8.8	11	4.6	22	29	49	8.7	4.6	22	29	49
18 - 44 YR.	3,990	3,967	99.4%	6.1	8.0	3.2	16	20	34	6.0	3.1	16	20	34
45+ YR.	4,198	4,184	99.7%	6.6	8.0	4.0	16	20	35	6.6	3.9	15	20	35
2+ YR.	12,000	11,956	99.6%	10	10	4.6	24	40	88	10	4.6	24	40	88
NAS SUBSTANCE 5072 : DIOCTYL SODIUM SULFOSUCCINATE														
SOURCE BY CATEGORY:		23(100%)												
				INTAKE IN MICROGRAMS PER KILOGRAM						INTAKE IN MICROGRAMS PER KILOGRAM				
0 - 5 MO.	62	2	3.2%	3.5	2.9	1.5	5.6	5.6	5.6	.11	-	-	-	5.6
6 - 23 MO.	275	98	35.6%	4.0	6.0	2.6	7.1	13	50	1.4	-	4.4	6.2	15
2 - 5 YR.	903	481	53.3%	3.7	4.2	2.5	8.1	11	20	2.0	.52	5.6	8.4	15
6 - 12 YR.	1,776	868	48.9%	2.2	2.7	1.5	4.7	6.7	11	1.1	-	3.3	4.7	9.3
13 - 17 YR.	1,133	398	35.1%	1.1	1.0	.74	2.6	3.2	4.5	.40	-	1.5	2.4	3.4
18 - 44 YR.	3,990	1,167	29.2%	.75	.91	.44	1.7	2.4	4.5	.22	-	.65	1.2	2.7
45+ YR.	4,198	480	11.4%	.66	.68	.42	1.6	2.0	3.1	.077	-	.15	.49	1.7
2+ YR.	12,000	3,394	28.3%	1.6	2.4	.76	3.6	5.5	11	.44	-	1.3	2.5	6.6
NAS SUBSTANCE 5076 : ETHOXYLATED MONO- AND DIGLYCERIDES (POLOXYETHYLENE (20) MONO- AND DIGLYCERIDES OF FATTY ACIDS)														
SOURCE BY CATEGORY:		01(100%)												
				INTAKE IN MILLIGRAMS PER KILOGRAM						INTAKE IN MILLIGRAMS PER KILOGRAM				
0 - 5 MO.	62	5	8.1%	.22	.088	.20	.38	.38	.38	.018	-	-	.18	.38
6 - 23 MO.	275	218	79.3%	1.9	1.3	1.8	3.6	4.3	5.7	1.5	1.4	3.4	4.2	5.7
2 - 5 YR.	903	901	99.8%	2.6	1.2	2.5	4.1	4.8	5.6	2.6	2.5	4.1	4.8	5.6
6 - 12 YR.	1,776	1,767	99.5%	2.0	1.0	1.8	3.2	3.7	5.2	2.0	1.8	3.2	3.7	5.2
13 - 17 YR.	1,133	1,124	99.2%	1.3	.60	1.2	2.1	2.4	3.1	1.3	1.2	2.0	2.4	3.1
18 - 44 YR.	3,990	3,970	99.5%	.94	.48	.87	1.6	1.8	2.3	.93	.87	1.6	1.8	2.3
45+ YR.	4,198	4,148	98.8%	.91	.50	.87	1.5	1.7	2.3	.90	.86	1.5	1.7	2.3
2+ YR.	12,000	11,910	99.2%	1.2	.66	1.0	2.3	3.0	4.3	1.2	1.0	2.3	3.0	4.3
NAS SUBSTANCE 5078 : ETHYL CELLULOSE														
SOURCE BY CATEGORY:		07(78%)	01(20%)	10(2%)										
				INTAKE IN MILLIGRAMS PER KILOGRAM						INTAKE IN MILLIGRAMS PER KILOGRAM				
0 - 5 MO.	62	5	8.1%	.0024	.0015	.0016	.0048	.0048	.0048	.00020	-	-	.0016	.0048
6 - 23 MO.	275	219	79.6%	.14	.72	.014	.029	.041	4.3	.11	.011	.028	.038	4.3
2 - 5 YR.	903	900	99.7%	.088	.48	.019	.034	.041	2.6	.087	.019	.034	.041	2.6
6 - 12 YR.	1,776	1,765	99.4%	.046	.25	.014	.026	.031	1.6	.046	.014	.026	.031	1.6
13 - 17 YR.	1,133	1,126	99.4%	.031	.16	.0094	.017	.021	.97	.031	.0094	.017	.021	.97
18 - 44 YR.	3,990	3,963	99.3%	.032	.18	.0066	.013	.015	.93	.032	.0065	.013	.015	.93
45+ YR.	4,198	4,125	98.3%	.038	.22	.0057	.011	.014	.99	.037	.0056	.011	.014	.99
2+ YR.	12,000	11,880	99.0%	.040	.24	.0076	.020	.028	1.1	.040	.0075	.020	.027	1.1

(-) VALUE = ZERO
(•) VALUE > ZERO

(**) NOTE: GREAT CAUTION MUST BE EXERCISED TO ENSURE THAT MEAN VALUES ARE NOT MISUSED (SEE INTRODUCTORY TEXT).

------NAS SUBSTANCES------
5071 5072 5076 5078

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FOOD ADDITIVES
SUMMARIZED DATA FROM NAS/NRC FOOD ADDITIVE SURVEYS

DIOCTYL SODIUM SULFOSUCCINATE
5072

REPORTED USE IN FOODS

TOTAL TONNAGE REPORTED 1976: 66.00
YEAR OF FIRST REPORTED USE: 1965

TECHNICAL EFFECTS:

P10 SURFACE TENSION CONTROL AGENT

FOOD CATEGORY	MEAN USUAL CONCENTRATION (%)	LOGS ≥25%	TECHNICAL EFFECTS
23 NON-ALCOHOLIC BVGS (B)	00.000059		P10

CONSUMER EXPOSURE

AGE GROUP	EATERS ONLY USUAL	EATERS ONLY 2SD	UNITS	% EATERS (CONCENTRATION)
0-5 MO	31	50		3.2
6-23 MO	43	80		35.6
2-5 YR	59	130		53.3
6-12 YR	62	140	MICROGRAMS	48.9
13-17 YR	62	150		35.1
18-44 YR	50	120		29.2
45+ YR	48	120		11.4
2+ YR	56	130		20.3

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000054

PB81-228595

FOOD ADDITIVES

Summarized Data from NRC Food Additives Surveys

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Subcommittee on Chemicals Used in Food Processing
Committee on Food Protection
Food and Nutrition Board
National Research Council

National Academy Press
Washington, D.C.
1981

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SPRINGFIELD, VA. 22161

1987 Poundages of Fatty Acid-based Emulsifiers

Name in Survey	NAS Code Number	CFR Citation	Pounds used by food industry
mono-and diglycerides	0130	184.1505	41,800,000
sodium stearoyl lactylate	1170	172.846	5,660,000
glyceryl monostearate	2527	182.1324	2,210,000
ethoxylated mono- and diglycerides	1070	172.834	1,380,000
polysorbate 60	2916	172.836 *et al*.	1,320,000
polysorbate 80	2917	172.840 *et al*.	1,160,000
propylene glycol stearate	2942	172.856	1,100,000
glyceryl-lacto esters of fatty acids	1088	172.852	662,000
diacetyl tartaric acid esters of mono- and diglycerides (DATEM)	0076	184.1101	652,000
propylene glycol mono- and diesters of fatty acids	1153	172.856 *et al*.	524,000
acetylated mono-glycerides	0530	172.828	451,000
calcium stearoyl lactylate	0538	172.844	330,000
sorbitan monostearate	3028	172.842 *et al*.	200,000
glycerol monooleate	2526	172.515	50,600
sodium stearyl fumerate	1156	172.826	10,300
polysorbate 20	2915	172.515	7,850

me in Survey	NAS Code Number	CFR Citation	Pounds used by food industry
oxystearin	1125	172.818 *et al.*	4,280
polysorbate 65	0535	172.838 *et al.*	3,730
succinylated monoglycerides	1176	172.830	3,240
monoglyceride citrate	0131	172.832	1,040
sodium lauryl sulfate	0347	172.822	1,000
monosodium phosphate derived mono- and diglycerides	0135	184.1521	830
sorbitan monooleate	8770	173.75	460
stearyl monoglyceride citrate	1175	172.755	no reported poundage
succistearin	1177	172.765	no reported poundage
ucrose fatty acid esters	1409	172.859	no reported poundage
lactylic esters of fatty acids	1102	172.848	no reported poundage
lactylic fatty acid esters of glycerol and propylene glycol	1101	172.850	no reported poundage
methyl glucoside -coconut oil ester	1114	172.816	no reported poundage

Total poundage all fatty acid-based emulsifiers: 57,532,330

* * * * *

Percent mono- and diglycerides of total:

Sum of mono- and diglycerides, for code numbers 0130, 2527 & 2526, is 44,060,600 pounds

$$\frac{44,060,600}{57,532,330} \times 100\% = 76.6\%$$

Additional Emulsifiers (incl. surfactants, etc.)

Name in Survey	NAS Code Number	CFR Citation	Pounds used by food industry
Sodium dodecyl-benzene sulfonate	1243	173.315	No reported poundage in 1987. (27,000 in other years).
dioctyl sodium sulfosuccinate	1066	172.810	71
sodium mono-and dimethyl naphthalene sulfonates	1165	172.824	No reported poundage
sodium lignosulfonate	1247	173.310	No reported poundage in 1987 (500 in other years
sodium methyl sulfonate	1404	173.385	No reported poundage
sodium n-alkylbenzene-sulfonate	1241	173.315	No reported poundage
sodium 2-ethylhexyl sulfate	1244	173.315	No reported poundage
sodium decylbenzene-sulfonate	1161	172.210	No reported poundage
polyoxyethylene (600) dioleate	1140	173.340	No reported poundage in 1987. (233,000 in other years).
polyoxyethylene (600) monoricinoleate	1141	173.340	No reported poundage

* * * * *

Total poundage all emulsifiers 57,532,401

Per capita 1987 USA intake of emulsifiers:

$$\frac{57{,}532{,}401 \text{ pounds}}{243 \text{ million people}} \times 454 \text{ grams/pound} \div 365 \text{ day/year} = 0.29 \text{ grams/day}$$

* * * * *

DSS fraction of emulsifier market:

$$\frac{71}{59{,}532{,}401} = 0.000001234 \text{ or } 1/810{,}316\text{th}$$

SUBMISSION EMA

AM

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September 3, 1998

VIA HAND DELIVERY

1998 SEP -4 P 11:58

Laura M. Tarantino, Ph.D.
Acting Director
Office of Premarket Approval
Food and Drug Administration (HFS-200)
200 C Street, S.W.
Washington, D.C. 20204

Re: GRAS Notification for DSS in Soft Drinks; Our File No. CY04825-05

Dear Dr. Tarantino:

On behalf of our client, Cytec Industries, we are submitting this clarification to the "intended use" section of the generally recognized as safe (GRAS) notification we submitted on July 20, 1998, regarding the safe use of dioctyl sodium sulfosuccinate (DSS) in flavor emulsions used in the production of carbonated and non-carbonated soft drinks. The original submission described the intended use of DSS "as a wetting agent or solubilizer for flavor emulsion stabilizers used in the production of carbonated and non-carbonated soft drinks." In reviewing this language, it became apparent that it could be interpreted as unduly limiting the purpose for which DSS may be added.

Accordingly, we are amending the intended use section of the GRAS Notification to describe the intended use of DSS as follows:

> A dispersing agent and stabilizer in flavor emulsions used in the production of carbonated and non-carbonated soft drinks.

This revised description clarifies and more accurately describes the function of DSS in the production of soft drinks.

Because the use level of DSS in the finished soft drink, 10 ppm, will not change, this revised description of the intended use will not affect the exposure and safety determinations contained in our previously submitted GRAS Notification. We have revised those sections of the Notification that contain a description of the intended use (the cover page, as well as pages 1,2, 9-10 and 15). For your convenience, we are enclosing three complete copies of this letter and the text section of the Notification (without Appendices) containing these revisions, as well as an additional copy of this letter for your use in acknowledging receipt.

Should you have any questions regarding this clarification of the intended use of DSS described in Cytec's GRAS Notification, please do not hesitate to contact me.

Cordially yours,

Ralph A. Simmons

Enclosures

cc: Randy Deskin, Ph.D., D.A.B.T.

Before the
FOOD AND DRUG ADMINISTRATION
Department of Health and Human Services
Washington, D.C.

GRAS NOTIFICATION

Name of Notifier:	Cytec Industries, Inc.
Post Office Address:	All communications on this matter are to be sent in care of Counsel for the Notifier, Ralph A. Simmons, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001. Telephone: (202) 434-4120.
Name of Substance and Intended Use:	Dioctyl sodium sulfosuccinate [CAS Reg. No. 577-11-7] for use as a dispersing agent and stabilizer in flavor emulsions used in the production of carbonated and noncarbonated soft drinks.
Dated:	September 3, 1998

Ralph A. Simmons
Counsel for Cytec Industries, Inc.

1. Claim of GRAS Status

(i) Name and Address of Notifier:

Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, New Jersey 07424

All communications on this matter are to be sent in care of Counsel for the Notifier, Ralph A. Simmons, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001. Telephone: (202) 434-4120.

(ii) Common or usual name of the notified substance:

Dioctyl sodium sulfosuccinate, or DSS

(iii) Applicable conditions of use:

As a dispersing agent and stabilizer in flavor emulsions used in the production of carbonated and noncarbonated soft drinks, for addition at levels equivalent to up to 10 parts per million (ppm) of the finished beverage as consumed.

(iv) Basis for GRAS determination

The described use of DSS has been shown to be generally recognized as safe (GRAS) through scientific procedures, as discussed more fully in the accompanying summary of the basis for the GRAS determination.

(v) Statement of availability of data

The data and information that are the basis for the GRAS determination are available for the Food and Drug Administration's review and copying or will be sent to FDA upon request.

Indeed, the Notifier believes that copies of all the relevant toxicological data are in the Agency's files.

* * *

The foregoing and attached information considered, it is respectfully submitted that the use of dioctyl sodium sulfosuccinate as a dispersing agent and stabilizer in flavor emulsions used in the production of carbonated and noncarbonated soft drinks, for addition at levels equivalent to up to 10 parts per million of the finished beverage in the form in which it is consumed, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because it is generally recognized as safe.

Respectfully submitted,

CYTEC INDUSTRIES, INC.

By_____
Ralph A. Simmons
Keller and Heckman LLP

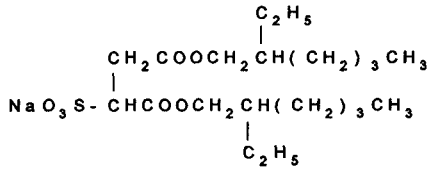
COUNSEL FOR THE NOTIFIER

2. Identity of the Notified Substance

Chemical Name: Dioctyl sodium sulfosuccinate; or, bis(2-ethylhexyl) sodium sulfosuccinate

CAS Registry No.: 577-11-7

Molecular and Structural Formulas: $C_{20}H_{37}O_7SNa$



Quantitative Composition: Complies with purity specifications set forth below.

Method of Manufacture: Produced by reaction of 2-ethylhexyl alcohol with maleic anhydride followed by addition of sodium bisulfite.

Characteristic properties: DSS is an anionic surface-active agent. It is a waxy white solid, soluble in many organic solvents. It dissolves slowly in water. DSS is stable in acid and neutral solutions, and hydrolyzes in alkaline solutions.

Food-Grade Specifications: DSS complies with the specifications set forth in the Food Chemicals Codex, 3d Ed. (1981), pp. 102-104. These include the following:

Assay	Not less than 98.5% $C_{20}H_{37}O_7SNa$, calculated on the dried basis.
Arsenic (as As)	Not more than 3 ppm
Bis(2-ethylhexyl)maleate	Not more than 0.4%
Clarity of solution	Passes test
Heavy metals (as Pb)	Not more than 10 ppm
Loss on drying	Not more than 2%
Residue on Ignition	Between 15.5% and 16.2%

3. Information on Self-Limiting Levels of Use:

In the applications described herein, DSS will be used in carbonated and noncarbonated soft drink beverages at levels that will not exceed 10 parts per million in the finished beverage. This is identical to the maximum level at which DSS is listed at 21 C.F.R. § 172.810 as a wetting agent in fumaric acid-acidulated dry beverage bases and fruit juice drinks. The 10 ppm maximum concentration is a well-established effective level for DSS in beverage products. The Notifier has not conducted testing to determine a level that would be self-limiting in the notified application.

4. Summary of Basis for GRAS Determination

A. Data and information relied on to establish safety

As indicated above, general recognition of safety in this instance is based on scientific procedures, in keeping with 21 C.F.R. § 170.30(b). As discussed more fully below, a large volume of toxicological data on DSS is available; these data have previously been reviewed by the Food and Drug Administration and an acceptable daily intake determined that is far in excess of that resulting from the notified use. The data have also been evaluated by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA), which also has published an acceptable daily intake that comfortably exceeds the intake calculated below. Consideration of cumulative intake from the currently cleared uses plus the notified use further confirms the safety of the additional use.

Toxicity of DSS and Acceptable Daily Intake

DSS is a surface-active agent that fulfills several unique, niche requirements in the food and pharmaceutical areas. The substance has been used in drug products since 1943. Its primary use in this area is in laxative preparations and fecal softeners. DSS has been used in food products since 1965. Due to its long-term use in these specific markets, numerous investigations have been conducted to determine the toxicological effects of extended exposure to ingested DSS. These data have been previously evaluated by both the Food and Drug Administration and by the Joint FAO/WHO Expert Committee on Food Additives. As part of its safety evaluation process, JECFA published a toxicological monograph on DSS. (*See* WHO Food Additives Series: 28, Toxicological evaluation of certain food additives and contaminants. Prepared by the 37th Meeting of the Joint FAO/WHO Expert Committee on Food Additives; World Health Organization, Geneva 1991.) A copy of the toxicological monograph appears as Appendix A to this notification.

A brief summary of the most relevant studies on DSS follows. In short-term testing, rats fed DSS for 4 weeks had no significant effects at dose levels up to 1%. Feeding DSS to rats for nine weeks at a 25% dietary concentration resulted in a decline in growth rate; the investigators suggested this was due to poor palatability, as food consumption was also decreased. DSS dosage at 2% and higher in the feed for 16 weeks also led to growth retardation, with virtually complete mortality at 4% or 8% in the feed. In a 24-week study, no adverse effects were observed when DSS was administered at levels up to 0.87 g/kg in the feed. Rats fed DSS for 26 weeks at levels up to 1.5% had no significant effects on weight gain and no adverse effects on

hematology, urinalysis, organ weights, or in organ histology. Thus, the 1.5% level appears to be the no-observed effect level (NOEL) for subchronic intake of DSS.

In chronic testing, rats receiving 1.0% DSS in the feed for two years had reduced body weight gain but no pathological changes upon gross and microscopic examination. A dose of 0.5% DSS in the feed was a NOEL in this study. Finally, in a one-year feeding study in dogs, a daily dose of 30 mg/kg did not result in any treatment-related signs of toxicity. No adverse effects were found upon gross and microscopic examination of G.I. tract organs and tissues, and serum enzyme analysis indicated no chronic liver toxicity.

It should be noted that both FDA and JECFA toxicological evaluators previously had concerns with regard to the potential for DSS to elicit adverse reproductive or teratological effects. This possibility has been extensively examined in several studies, most notably in a multigeneration reproduction study that was conducted at the request of a Scientific Review Panel convened by FDA in 1984 with the purpose of evaluating the safety of DSS for pharmaceutical and food uses. Upon review of the full report of the three-generation study, the FDA evaluators concurred with the investigators' conclusions that the no-observable effect level for DSS, when administered in the diets of rats for three successive generations, is 0.1% for body weight loss of parental animals and offspring, with a NOEL for reproductive parameters of 1.0%. The FDA toxicologists also concluded that reduced pup survivability observed in some litters at the 1.0% dose level was a spurious finding that was not directly related to treatment with DSS. Thus, in this study as well as the others summarized above, the NOEL for DSS administration,

0.1% in the diet, was based solely on a reduction in body weights for parental animals and pups.[1/] The conclusions reached by JECFA in the appended monograph are substantively identical to FDA's.

The studies discussed above, and several others addressed in the JECFA monograph, are summarized in Table 1 below. Complete references are given in the monograph set forth in Appendix A.

Table 1
Subchronic and Chronic Feeding Studies on DSS

Study	Spp	Duration	Route	NOEL	Effects	Pathology
Guerrant, 1937	Rat	9 wk	diet		Single dose (25%), b.w. ↓	
Benaglia, 1943	Rat	24 wk	diet	>0.87g/kg		Yes
Fitzhugh & Nelson, 1948	Rat	16 wk	diet	<2%	b.w.↓	
Hazelton, 1958	Rat	28 day	diet	>1%	single dose	
Taylor, 1966	Rat	26 wk	diet	>1.5%		Yes
Fitzhugh & Nelson, 1948	Rat	2 yr	diet	0.5%	b.w.↓ at 1%	Yes
Benaglia, 1943	Rbt	24 wk	IG	>0.124g/kg	single dose	Yes
Case, 1977	Dog	1 yr	gav	>30 mg/kg	single dose	Yes
Benaglia, 1943	GP	15 mos	water	>1g/L	single dose	
Amer. Cyanamid, 1970	Rat	repro	diet	lact:<0.5% terato>1%	pup b.w.↓ due to palatability	

1/ *See* FDA Memoranda, dated September 12, 1986, and May 19, 1987, from Charles V. Frazier, Team Leader, Standards and Monitoring Branch, to Lawrence Lin, Ph.D., Direct Additives Branch. For the Agency's ready reference, copies of both memoranda appear as Appendix B to this notification.

Hoechst Roussel, 1976	Rat	terato	diet	terato: 1%	maternal b.w.↓ at 2%	
Hoechst Roussel, 1979	Rat	terato	diet		single dose	
MacKenzie, 1990	Rat	repro	diet	tox: 0.1% repro: >1%	b.w.↓ at 0.5 and 1%	

Notes: Spp = Species; Rbt = Rabbit; GP = guinea pig; repro = reproductive toxicity study, terato = teratology study (under "Duration" heading); IG = intragastric; gav = gavage; water = drinking water; NOEL = no-observed effect level; lact = lactation effect; terato = teratological effect, repro = reproductive effect (under "NOEL" heading); b.w.↓ = decline in body weight gain; Pathology = Pathology conducted on primary organs.

It is apparent from the foregoing that the "effect" on the basis of which the no-observed effect levels for the various studies were established is the observation of a decline in body weight growth only. Other effects associated with changes in organ weight or histopathological observations were not found.

The acceptable daily intake (ADI) for DSS is determined by applying a suitable safety factor to the NOEL established in the feeding studies. Generally, when long-term testing has been conducted, a 100-fold safety factor is applied to the NOEL from the chronic toxicity studies. In the case at hand, the NOEL for chronic intake of DSS in the diet is 0.5%; this would support an ADI of 0.005% (50 ppm). Although the NOEL established in the multigeneration study, 0.1% in the feed, is somewhat lower than the chronic value, use of the higher NOEL would be reasonable here since the two-year study reflects the results of chronic intake over the lifetime of the test animals while the multigeneration study is designed to study the effect of DSS at a limited phase of life in which the animals are most vulnerable.

This fact notwithstanding, both the FDA and JECFA evaluators chose to rely on the NOEL from the reproductive toxicity study to set their respective ADIs. This was due to the general practice of employing the lowest available ADI, and also to the fact that the multigeneration study reflects more current toxicity testing standards than the older chronic feeding study.

The NOEL from the multigeneration reproductive study, 0.1% in the diet, is equivalent to an ingestion level of 50-150 mg/kgbw/day. In keeping with its usual practice for studies of this duration, FDA established its ADI by applying a 100-fold safety factor to the NOEL, thus calculating an ADI of 0.5 mg/kgbw/day. In its determination, because of the lack of a recent chronic study, JECFA applied a more conservative safety factor of 500, to reach an ADI of up to 0.1 mg/kgbw/day for DSS. (*See* WHO Technical Report Series 859, Evaluation of certain food additives and contaminants. Forty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives; World Health Organization, Geneva.) Based on the standard individual body weight of 60 kg, FDA's ADI for DSS is equivalent to intake of 30 mg/person/day; the JECFA ADI equates to intake of 6 mg/person/day.

Intake of DSS From Notified Use

As indicated above, the use of DSS dealt with here is in the preparation of flavor emulsions used in the production of carbonated and noncarbonated soft drinks. These beverages are generally prepared by combining water and carbon dioxide (for the carbonated drinks) with a syrup that contains concentrated flavoring emulsion, sweeteners, and other ingredients. The flavor emulsion used in the preparation of the syrup must be stable at any stage of the

manufacturing process to prevent separation of the flavor oils upon dilution with water. Thus, emulsion stabilizers are used to prepare the flavor concentrate in a stable form. Use of DSS facilitates this process by functioning as a wetting, or solubilizing agent, for the emulsion stabilizer. In this application, as in other beverage uses, DSS will be employed only at very low levels, with a maximum addition level equivalent to 10 ppm in the finished beverage as consumed.

For the sake of conservatism in calculating the potential intake of DSS resulting from this use, we will assume that it will be employed at the maximum anticipated level of 10 ppm in all soft drinks. Data on individual intake of such beverages is available in the U.S. Department of Agriculture's (USDA) study, "Foods Commonly Eaten by Individuals: Amount per Day and Per Eating Occasion" (March 1982, reviewed and approved for reprinting February 1990). Based on the reporting of food consumed by participants in a three-day survey, the USDA study found that the daily level of consumption of carbonated soft drinks by the 90th percentile consumer of these products is 556 g/person/day (or, about 0.56 kg/person/day).[2/] If DSS is present in these beverages at a concentration of 10 ppm, or 10 milligrams per kilogram, the daily intake of DSS by the 90th percentile consumer will be 5.6 mg/person/day. We note that this value necessarily

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[2/] USDA also recorded consumption data for noncarbonated soft drinks. The survey report states that most of such beverages consumed were prepared from powdered mixes. Beverages prepared from dry mixes are not included in the use for which this notification is submitted; indeed, DSS is currently permitted for this use under 21 C.F.R. § 172.810. Thus, the consumption data for noncarbonated soft drinks are not included here. Considering the inherently conservative nature of the USDA survey for estimating food intake, and since noncarbonated beverages will, at least to some extent, be consumed in place of carbonated beverages, the 90th percentile intake value for carbonated soft drinks is believed to be a reasonable estimate of consumption of the beverages of interest here.

exaggerates actual intake since it is based on the assumptions that DSS will be used in all soft drinks and is always present at the maximum anticipated use level of 10 ppm. In addition, the 3-day survey procedure used by USDA will tend to result in a high estimate of individual food intake over extended periods of time because of the short duration of the survey.

Cumulative Intake of DSS

The sources of intake of DSS fall into two overall categories: food and drugs. Pharmaceutical applications for DSS include laxative formulations, stool softener products, and vitamin/mineral supplements. The primary use is believed to be in stool softeners, which are used only infrequently and, thus, do not represent a source of chronic exposure. Use of DSS in supplements is primarily in high-iron products which likewise are directed towards short-term use, *e.g.*, during pregnancy or to treat anemia. Thus, chronic ingestion of DSS is expected to result almost exclusively from its use in food.

Use of DSS in the food sector has occurred for a sufficiently long period (since 1965) to permit calculation of the actual level of intake resulting from the existing uses. The United States (the National Research Council, on behalf of FDA) sponsors periodic surveys of food additive use, which provide data on the actual quantities of added substances going into food applications. The principal survey for trends in food additive usage is the recording of total poundage for substances used by the food industry; five such surveys have been conducted, in 1970, 1975, 1976, 1982, and 1987. Information on food use of DSS was reported in the last three surveys (see Appendix C). As shown there, the per capita intake for DSS from food uses varied from 0.6 to 2 micrograms per person per day (μg/day).

In 1977, FDA sponsored a more detailed survey of the food industry with regard to specific food uses and levels of addition for substances used in food. While FDA regulations permit use of DSS in a number of foods including drinks and desserts prepared from dry mix, cocoa beverages, and foods containing gums, the survey found it used only in beverages made from dry mixes (see Appendix C). Further, even though the regulation clears DSS for this use at levels of up to 10 mg/kg (ppm), the actual reported DSS use level was only 0.59 mg/kg, far below the cleared level.

The data from the 1977 survey were also combined with information from a survey of food intake to derive additive intakes for high-percentile consumers of the foods that contain the additives. For the reported use of DSS in 1977, the mean age-weighted DSS intake for individuals over two years of age was 56 μg/day; the 90th percentile consumer's intake was 130 μg/day. These intake estimates make use of the exaggerative assumption that DSS is used in *all* beverages consumed and, thus, may be viewed as very conservative estimates of intake from the uses that have been permitted to date.

The long history of practical experience with marketing of DSS in the food industry suggests that the substance will be used in selected "niche" markets in which it excels relative to other emulsifiers. Indeed, 1987 poundage data for all emulsifiers indicate a total market of 58 million pounds, for a per capita intake of 300 mg/day. The 1987 use of DSS in the food supply represents just 1/810,000 of the total emulsifier market (see Appendix C).

The maximum estimated intake level given above for current uses of DSS in food is 130 μg/day, or 0.13 mg/day. Cumulative intake of DSS from all food uses, therefore, will not exceed

the total of this value and the 5.6 mg/day intake conservatively calculated above for soft drink use, or about 5.7 mg/day. This is below the ADI set by JECFA for DSS, and is only a small fraction of the ADI established by FDA.

B. Information unfavorable to the GRAS determination

The Notifier is not aware of any reports of investigations or other information that might appear to be inconsistent with the GRAS determination.

C. Basis for concluding that the notified use of DSS is GRAS

FDA describes the criteria for determining GRAS status for a particular use of a substance through scientific procedures under 21 C.F.R. § 170.30(a) and (b). Section 170.30(a) states that general recognition of safety must be based on the views of experts qualified by scientific training and experience to assess the safety of substances added to food. In the case at hand, two well-qualified bodies of experts, FDA and JECFA, have evaluated the data available on DSS and have established intake levels that the respective experts consider to be safe based on these data. Even based solely on the more conservative conclusions of JECFA, the notified use of DSS is safe by reference to the ADI.

GRAS status must also be based on common knowledge throughout the relevant scientific community that the substance is not harmful under the conditions of intended use. The thorough evaluation of the safety of DSS conducted by JECFA involved the participation of scientific experts from both the United States and the international community, and the results of

the evaluation were published through the usual FAO/WHO mechanism. Clearly, there is wide acceptance in the scientific community knowledgeable about the safety of substances added to food that DSS may be safely used in food at the levels contemplated here.

Section 170.30(b) states that general recognition of safety based on scientific procedures requires the same amount and quality of scientific evidence as that required to obtain clearance as a food additive. In establishing their respective ADIs, FDA and JECFA both relied on well-established scientific standards and procedures for assessing the safety of substances added to food. The level of intake of DSS considered acceptable by both expert bodies, based on full consideration of the quality and quantity of available data, is above the cumulative level of intake of DSS in food as a result of the notified use. Finally, FDA states that GRAS determinations based on scientific procedures shall be based on generally accepted and available data, information, etc., that ordinarily are published but may also be corroborated by unpublished information. Much of the toxicological data have been published in widely disseminated journals. (See full references given in the monograph set forth in Appendix A.) Notably, these include results of the two-year chronic feeding study in rats and one-year feeding study in dogs, and the multigeneration reproduction study in rats. The latter study provided the key data based on which the FDA and JECFA ADIs were established. Moreover, the publication of the JECFA monograph and the basis for establishment of its ADI further disseminated the publicly available data supporting the general recognition of safety of DSS in the application that is the subject of this notification.

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Considering the foregoing, we respectfully submit that all criteria for general recognition of safety based on scientific procedures are met and, thus, that dioctyl sodium sulfosuccinate is generally recognized as safe for use as a dispersing agent and stabilizer in flavor emulsions used in the production of carbonated and noncarbonated soft drinks at levels equivalent to up to 10 parts per million of the finished beverage.

Reference List for Industry Submission, GRN 000006

Pages	*Author*	*Title*	*Publish Date*	*Publisher*	*BIB_Info*
000020 - 000034	Lin FSD	Dioctyl Sodium Sulfosuccinate	1991	Toxicological evaluation of certain food additives and contaminants	WHO Food Additives Series:28

NA- Not applicable