UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: June 30, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessments: Two Exemption from the Requirement of a Tolerance for Sodium Dioctyl Sulfosuccinate (CAS Reg. No. 577-11-7)

FROM: Pauline Wagner, Chief Pauline Wagner 7/5/06
Inert Ingredient Assessment Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of two inert ingredient exemptions from the requirement of a tolerance. Current exemptions are to be maintained.

Chemical: Sodium Dioctyl Sulfosuccinate

Table 1. Tolerance Exemptions Expression

40 CFR	Inert Ingredients	Limits	Uses (Pesticidal)	CAS Reg. No. and Names
180.910	Sodium dioctylsulfosuccinate	None	Surfactants, related adjuvants of surfactants	577-11-7 Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester,sodium salt
180.930				

Use Summary: Sodium dioctylsulfosuccinate is used as a wetting agent in industrial, pharmaceutical, cosmetic & food applications. It is a dispersing and solubilizing agent in foods and an adjuvant in tablet formation, also. As an inert ingredient, sodium dioctylsulfosuccinate is used as a surfactant or related adjuvant of surfactants in pesticide formulations applied to growing crops, raw agricultural commodities, and animals.

Background: The EPA recently reviewed the antimicrobial use of sodium dioctylsulfosuccinate, and the toxicological conclusions from that assessment also apply to the inert ingredient uses of the chemical under 40 CFR 180.910 and 180.930. However, the safety findings for the inert ingredient uses of sodium dioctylsulfosuccinate were inadvertently omitted from the assessment and are being addressed here. The full risk assessment for sodium dioctylsulfosuccinate is attached to this action memo.

Human Health Risk Characterization: Based on the risk conclusions determined in the antimicrobial risk assessment on sodium dioctylsulfosuccinate, there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure when considering dietary exposure and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of sodium dioctylsulfosuccinate when used under 40 CFR 180.910 and 40 CFR 180.930 can be considered reassessed as safe under section 408(q) of the FFDCA.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two exemptions from the requirement of a tolerance for the inert ingredient sodium dioctylsulfosuccinate. I consider the two exemptions established in 40 CFR 180.910 and 180.930 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi

Lois A. Rossi, Director
Registration Division

Date: July 7, 2006

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 28, 2004

MEMORANDUM

SUBJECT: Butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt: Tolerance Reassessment Decision Document PC Codes 079027; 790130

FROM: Laura E. Bailey
Senior Environmental Scientist/Special Assistant
Antimicrobials Division (7510C)

TO: Frank T. Sanders, Director
Antimicrobials Division (7510C)

THRU: Jack Housenger, Associate Director
Antimicrobials Division (7510C)

Attached is the science assessment which summarizes the Agency's decision on the tolerance reassessment for butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt. Butanedioic acid, sulfo-, 1,4-dioctyl ester, sodium salt (generically known as dioctyl sodium sulfosuccinate) was presented to and peer-reviewed by the Lower Risk Pesticide Chemical Focus Group (LRPFG) on June 22, 2004. Revisions were made to the original assessment subsequent to the committee meeting. This document summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity for butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt.

In performing this assessment, EPA has utilized reviews published by the International Programme on Chemical Safety/ World Health Organization (IPCS/WHO), the Food and Agriculture Organization of the United Nations (FAO), and a report submitted by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Sulfosuccinates Group under the High Production Volume (HPV) Challenge Program. Information obtained from the Hazardous Substances Databank (HSDB) was also used in this assessment.

I. Executive Summary:

Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is an active ingredient in food-contact sanitizing solutions and in pet shampoos used for flea control. It is also an inert ingredient in a number of end-use products used on a variety of crops. Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is listed in EPA's List 4B (available on the internet epa.gov/opprd001/inerts/lists.html), which includes inert ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment. This chemical is also currently approved for use as a food additive in 21 CFR 172.810.

During the recent transfer of the Food and Drug Administration's (FDA's) 21 CFR 178.1010 to EPA's section of the Federal Register, the chemical name dioctyl sulfosuccinate, sodium salt was believed to be the straight chain (unbranched) eight carbon form of octyl. Thus, the chemical name and CAS number now established under 40 CFR 180.940(c) are butanedioic acid, sulfo-, 1,4-dioctyl-ester, sodium salt and CAS No. 1639-66-3. However, octyl can be used generically for branched forms which also contain eight carbons. The Agency now believes that the term dioctyl was used to represent the branched chain of eight carbons known as ethylhexyl. The ethylhexyl form of dioctyl sulfosuccinate, sodium salt is known as butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt chemical and CAS No. 577-11-7. Both chemicals are located in the publicly available list of inert ingredients that may be used in pesticide products. The names of the tolerance exemptions in 40 CFR 180.910, 930, and 940(c) must be revised to account for this new understanding. This reassessment thus supports only CAS. No. 577-11-7; butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt. The publicly available data indicates that the form of dioctyl sodium sulfosuccinate (DSS) considered is CAS No. 577-11-7, the ethylhexyl form. Therefore, when DSS is mentioned throughout this document it is representative of the ethylhexyl form.

Toxicity data for DSS were obtained from published studies summarized in two reports of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and in a report submitted to the EPA HPV Challenge Program by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Sulfosuccinates Group. Information obtained from the Hazardous Substances Databank (HSDB) was also used in this assessment. Acute toxicity data from animal studies indicate low oral and dermal toxicity for DSS. Reproductive toxicity studies, on the other hand, showed effects on lactation and parental body weight and weanling pup weight at high dietary levels [0.5% (5 g/kg)], but no adverse effects on reproductive function in the test animals. In developmental toxicity studies, 2% DSS in the diet (20,000 mg/kg) caused adverse effects on the fetuses, including exencephaly and increased skeletal abnormalities. These effects were observed at high dose levels that also caused maternal toxicity.

Exposure to butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt may occur through FDA-approved uses, or through its use in products such as stool softeners and laxatives. Use of butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt in pesticide products for

agricultural applications and in food-contact sanitizing solutions is expected to result in much lower exposure than the FDA-regulated uses of this compound, as well as lower exposure than the use in stool softeners and laxatives. Exposures from the known uses of butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt are expected to result in human exposure below a dose level that may possibly produce any adverse effects.

Taking into consideration all available information on butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt, including its low acute toxicity via oral and dermal routes, its safe uses as a food additive and ingredient in pharmaceutical products, the observation of reproductive and developmental effects only at very high dose levels, and its uses in agricultural pesticide products and in food-contact sanitizing solutions, there is a reasonable certainty that no harm will occur to the general public or any population subgroup from aggregate exposure.

II. Use Information:

The tolerance exemptions being reassessed in this document, the 40 CFR location of the established exemption from the requirement of a tolerance and the use pattern as an inert and active ingredient are listed in Table 1.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Tolerance Exemption Expression	CAS No.	40 CFR	Use Pattern	Limits
Sodium dioctyl sulfosuccinate	577-11-7	180.910[2]	Surfactants, related adjuvants of surfactants	None
Sodium dioctyl sulfosuccinate	577-11-7	180.930[3]	Surfactants, related adjuvants of surfactants	None
Butanedioic Acid, Sulfo-, 1,4-dioctyl Ester, Sodium Salt[1]	1639-66-3 [1]	180.940(c)[4]	Food-contact surface sanitizing solutions	None

1. It should be noted that in transferring FDA's 21 CFR 178.1010 to EPA's section of the Federal Register, the term dioctyl sulfosuccinate, sodium salt was thought to be the chemical names and CAS numbers listed under 40 CFR 180.940(c). The term dioctyl was used instead of ethylhexyl. The names of the tolerance exemptions in 40 CFR 180.910, 930, and 940(c) must be revised to account for this nomenclature change (CAS. No. 577-11-7 butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt).
2. Residues of chemical substances listed in Sec. 180.910 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.
3. Residues of chemical substances listed in Sec. 180.930 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.
4. Residues of chemical substances listed in Sec. 180.940 are exempted from the requirement of a tolerance when

used in accordance with good manufacturing practice as ingredients in an antimicrobial pesticide formulation, provided that the chemical substance is applied on a semi-permanent or permanent food-contact surface (other than being applied on food packaging) with adequate draining before contact with food. Under 180.940 (c), chemical substances when used as ingredients in an antimicrobial pesticide formulation may be applied to food-processing equipment and utensils.

Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is listed under List 4B, which includes inert ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment. Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is sponsored by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Sulfosuccinates Group under the High Production Volume (HPV) Challenge Program. HPV chemicals are those that are manufactured or imported into the United States in volumes greater than one million pounds per year. There are approximately 3,000 HPV chemicals that are produced or imported into the United States. The HPV Challenge Program is a voluntary partnership between industry, environmental groups, and the EPA which invites chemical manufacturers and importers to provide basic hazard data on the HPV chemicals they produce/import. The goal of this program is to facilitate the public's right-to-know about the potential hazards of chemicals found in their environment, their homes, their workplace, and in consumer products.

Active and Inert Uses:

According to the EPA's OPPIN database, butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is registered as an active ingredient in two end-use products used as pet shampoos for flea control (PC code 079027), for which there are 2 active labels. Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is also an inert ingredient (PC code 790130) in over 700 end-use products, including products used on a variety of crops.

FDA-approved Uses:

Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is currently approved for use as a food additive in 21 CFR 172.810, as a wetting agent in fumaric acid-acidulated foods, as a processing aid in the production of unrefined cane sugar, as a solubilizing agent on gums and hydrophilic colloids, as an emulsifying agent for cocoa fat, and as a dispersing agent in cocoa. It is also used as a dispersing agent and stabilizer in flavor emulsions used in the production of carbonated and non-carbonated soft drinks. Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is listed in 20 CFR 131.130 as a solubilizing agent for use in evaporated milk.

Other Uses:

Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is used in pharmaceutical products such as stool softener and laxatives. The suggested daily labeled dosage for over-the-

counter products containing butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt used for stool softening is 100 to 300 milligrams active ingredient for adults, and 100 milligrams active ingredient for children 2 to 12 years of age.

III. Physical/Chemical Properties:

Butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt is a white waxy solid that is soluble in many organic solvents and in water. It is an anionic surface active compound with marked wetting characteristics. The chemical structure and physical/chemical properties of butanedioic acid, sulfo-1,4-bis (2-ethylhexyl) ester, sodium salt, as reported in Chemfinder, HSDB, and the SOCMA Test Plan are presented in Table 2.

Table 2. Chemical Structure and Physical/Chemical Properties of Dioctyl Sodium Sulfosuccinate

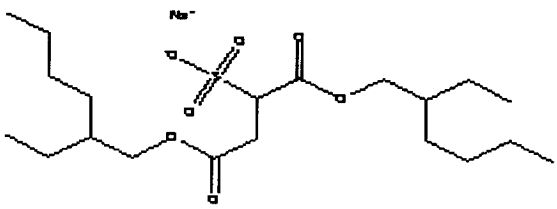
Chemical Structure	
Chemical Name	Bis(2-ethylhexyl) sodium sulfosuccinate
Synonym(s)	Aerosol OT; Alphasol OT; Bis(2-ethylhexyl) S-sodium Sulfosuccinate; 1,4-bis(2-ethylhexyl) Sodium Sulfosuccinate; Bis(2-ethylhexyl) Sodium Sulfosuccinate; Bis(2-ethylhexyl) Sulfosuccinate Sodium Salt; Butanedioic Acid, Sulfo-, 1,4-bis(2-ethylhexyl) Ester, Sodium Salt; Colace; Complemix; Constonate; Coprol; Dioctlyn; Dioctylal; Dioctyl-medo Forte; Generically known as Dioctyl Sodium Sulfosuccinate; Diomedicone; Diosuccin; Diotilan; Diovac; Diox; Disonate; Doxinate; Doxol; Butanedioic acid, sulfo-, 1,4-dioctyl ester, sodium salt; Dulsivac; Duosol; Konlax; Kosate; Laxinate; Manoxol OT; Molatoc; Molcer; Molofac; Monawet Md 70e; Nevax; Norval; Regutol
CAS No.	577-11-7
Molecular Formula	$C_{20}H_{38}O_7S.Na$
Molecular Weight	445.56
Physical State	White, wax-like solid with a characteristic odor
Melting Point (°C)	153-157 (measured)

Table 2. Chemical Structure and Physical/Chemical Properties of Dioctyl Sodium Sulfosuccinate	
Water Solubility	15 g/L at 25 °C
pH	Not available
Density/Specific Gravity	Not available
Vapor Density	Not available
Estimated Vapor Pressure	2.17×10^{-11} mm Hg at 25 °C
Estimated Octanol/Water Coefficient	Not available
Dissociation Constant	Not available
Estimated Henry's Law constant	5×10^{-12} atm-m^3/mol
Estimated Soil Sorption Coefficient (Koc)	9.37 - 1041

IV. Hazard Assessment:

Toxicological data for DSS are presented in Tables 3 and 4. These data were obtained from published studies summarized in two reports of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and in a report submitted to the EPA HPV Challenge Program by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Sulfosuccinates Group.

In 1974, JECFA published a report entitled "Toxicological Evaluation of Some Food Colours, Enzymes, Flavour Enhancers, Thickening Agents, and Certain Food Additives", which included toxicity information on DSS. An update to the JECFA report was issued in 1991. The updated report summarized the 1974 FAO/WHO report and provided additional toxicological data on DSS that became available since 1974. The additional information includes a chronic toxicity study in rats, a new reproductive study on rats, and two inhalation studies. Additionally, the structure of the chemical evaluated in the report is the ethylhexyl form.

The Synthetic Organic Chemical Manufacturers Association (SOCMA) Sulfosuccinates Group submitted a report on sulfosuccinates in 2001 under the HPV Challenge Program. The report, entitled HPV Test Plan for Sulfosuccinates, includes information on the physicochemical properties, environmental fate, ecotoxicity and human health data of sulfosuccinates, including DSS. It is noted that there is no indication of a peer-review process for SOCMA's data.

Table 3. Acute Toxicity of Dioctyl Sodium Sulfosuccinate	
Species	**LD_{50}**
Acute Oral Toxicity	
Mouse	4.8 g/k-gm
Mouse	2.64 g/kg
Mouse	1.50 g/kg
Rat	3.98 g/kg
Rat	1.80 g/kg
Rat	4.3 g/kg
Rat	3.08 g/kg
Rat	7.5 mL/kg*
Rat	5.7 g/kg*
Rat	4.2 mL/kg**
Acute Dermal Toxicity	
Rabbit	> 10 g/kg

* Compound tested was Aerosol/OT-80 PG which consists of 80% DSS, 20%, propylene glycol solvent and less than 1% sodium sulfate.
** Compound tested was Aerosol OT-100 which consists of 100% DSS.

Table 4. Subchronic, Chronic, Genetic, Reproductive and Developmental Toxicity Data for Dioctyl Sodium Sulfosuccinate		
Study	**Species**	**Results**
Subchronic Toxicity		
16-week feeding study	Rats	NOAEL < 2% dietary (20,000 mg/kg)
26-week feeding study	Rats	NOAEL = 0.5% dietary (5,000 mg/kg)
1-year gavage study	Dogs	NOAEL ≥30 mg/kg
Chronic Toxicity		
2-year feeding study	Rats	NOAEL = 0.5 % dietary (5,000 mg/kg)

Table 4. Subchronic, Chronic, Genetic, Reproductive and Developmental Toxicity Data for Dioctyl Sodium Sulfosuccinate		
Study	**Species**	**Results**
Genetic Toxicity		
Ames test	--	Negative (Salmonella strains TA98, TA100, TA102, TA1535 and TA1537)
Chromosomal aberration assay	--	Positive only at cytotoxic concentrations
Reproductive Toxicity		
Three-generation reproductive toxicity study	Rats	NOAEL <0.5% dietary (5,000 mg/kg) - Effects on lactation at 0.5%.
Three-generation reproductive toxicity study	Rats	NOAEL = 0.1% dietary (1,000 mg/kg) - Effects on parental body weight and pup weight at 0.5% NOAEL > 1% dietary (10,000 mg/kg) - No effects on reproduction at doses tested
Developmental Toxicity		
Developmental Toxicity	Rats	Developmental NOAEL = 1% (10,000 mg/kg) - Exencephaly at 2% (20,000 mg/kg)
Developmental Toxicity	Rats	Developmental NOAEL < 2% (20,000 mg/kg) - Decreased fetal weights and crown-rump lengths. Maternal NOEL < 2% (20,000 mg/kg) - Decreased maternal food consumption and weight gain

Acute toxicity

The 1991 JECFA report concluded that DSS is practically nontoxic when given orally to mice and rats based on the results of acute toxicity studies. The report noted that "[i]n most cases, the gross pathological examination did not reveal any observable lesions except that the gastrointestinal tract of some animals that died were filled with clear fluid. In addition, some animals had diarrhoea or showed signs of intestinal irritation."

Subchronic, Chronic, Genetic, Reproductive and Developmental Toxicity

The following information describes the toxicity studies listed in Table 4 and additional studies included in the 1991 JECFA report. The information was extracted directly from Section 2 (Biological Data) of that report.

Short-term studies

"In a 9-week study rats that received 25% of DSS in the diet showed a decrease in growth rate. The authors suggested that this effect was due to impalatability of the DSS treated

diet since this group showed a decrease in food consumption. Necropsy revealed no visible lesions in the G.I. tract."

"Groups of five male and five female rats were given 0, 0.19, 0.37, 0.55, 0.75, and 0.87 g/kg of DSS in their diet for 24 weeks. No deaths occurred but there was some initial lag in body weight gain compared to the controls. No significant hematological effects were noted. Histology of the liver, spleen, kidney, pancreas, stomach, and gut, bladder, gonads, heart, lung, brain and spinal cord showed nothing remarkable."
"Groups of five male weanling rats were given diets containing 0, 2%, 4%, and 8% DSS for 16 weeks. There was marked growth retardation at the 2% level without mortality, but only one animal survived at 4% and all animals died within one week at the 8% level from severe gastrointestinal disturbances."

"[G]roups of 12 male and 12 female weanling rats were provided with diets containing 0, 0.5% 1.04% and 1.5% DSS for 26 weeks. There were no significant differences between test and control groups regarding body weight gain with the exception of female animals which showed some slight reduction at the 1.0% and 1.5% level during the third week. No adverse effects appeared in the findings of hematology, urinalysis, food consumption, the weight of spleen, liver, adrenal, kidney, gonads, or in the histology of the heart, lung, liver, spleen, kidney, adrenal, bladder, thyroid, pancreas, lymph nodes, gut, muscle, bone, marrow, gonads and thymus. Two controls and four test animals in the 1.5% group died, two of the latter from hemorrhagic gastroenteritis."

"Seven rabbits were given intragastrically 0.124 g DSS/kg bw daily for 24 weeks. Higher doses were not tolerated because of gastrointestinal irritation. No abnormal pathological findings were seen on gross and histopathological examination of the liver, spleen, pancreas, kidney, gut, bladder, gonads, heart, lung and CNS."

"Three monkeys were given intragastrically 0.125 g DSS/kg bw daily for 24 weeks. Higher doses were not tolerated because of gastrointestinal irritation. No abnormal pathological findings were seen on gross and histopathological examination of the liver, spleen, and pancreas, kidney, gut, bladder, gonads, heart, lung and CNS."

"When 4 male and 4 female Beagle dogs were given 30 mg/kg doses of DSS via gavage for a period of one year, no treatment-related signs of toxicity were observed at any period when the dogs were examined. Gross and microscopic examination of tissues and organs of the G.I. tract did not reveal any toxic changes, nor were there any serum enzyme changes indicative of chronic liver toxicity."

"Groups of 3 guinea pigs were given 0.1, 0.5, and 1.0 g/1 solutions of DSS (Alphosol OT) as a replacement for drinking water for a period of 15 months. The growth rate of the animals was not affected, once they were adjusted to the taste of DSS. Necropsies did not reveal any pathological alterations in organs and tissues of the treated animals."

Chronic Toxicity

"Groups of 12 male and 12 female weanling rats were given 0, 0.25%, 0.5% and 1.0% DSS in their diet for two years. Body weight gain was slightly reduced in the 1% test group during the first three months and became more pronounced during the first year. No pathological changes were noted at gross examination or in the histology of lung, heart, liver, spleen, pancreas, stomach and gut, kidney, adrenal, testes, thyroid, parathyroid, lymph nodes, bone, muscle, and marrow."

Tumor Promotion Studies

"When given orally to inbred Charles River Fischer 344 rats as 1.0% of the diet, DSS exhibited no promotional activity in rats treated with s.c. injections of 1,2,-dimethylhydrazine (DMH) at 20 mg/kg/wk for 20 weeks. Reducing the dose of DMH to 10 mg/kg/wk decreased significantly the number of gastrointestinal tumors per rat in the DSS treated group at the 5th and 6th month necropsies." [Note: s.c. = sub cutaneous]

Developmental /Reproductive Toxicity

"DSS was fed in the diet to groups of 40 male and 40 female rats (Carworth Farms, CFE strain) for three successive generations at levels of 0, 0.5, or 1.0% . . . The first mating of the F_0 generation and F_2 generation (dams continuously fed DSS and pups weaned to test diet), resulted in fertility indices and gestation indices that were high and comparable. The viability index was good, but slightly depressed for F_{3b} pups. The lactation index was depressed for both of these matings (64, 46, 42 for F_{1a} pups at 0, 0.5, 1.0% test diet respectively, and 71, 59, 53 for F_{3b} pups for the respective diets). Also, for these groups, mean weight of pups decreased with increasing concentrations of DSS in the diet of the dams. For the other three matings (F_{1b}, F_2, F_{3a} pups), the viability and lactation indices and the mean weight of pups from dams on test diets were less than those of control for the F_{1b} pups, but similar to controls for the F_2 and F_{3a} pups. The lowering of survival rate and mean body weight of F_{3b} pups was attributed to impairment of nutrition, because of the taste of DSS secreted in the milk of the dams. Autopsy and skeletal studies of the pups indicated no significant changes, with the exception of the occasional presence of an extra vertebra in the sternum between the fifth and sixth sternebrae (1/29, 7/30, and 4/29 at 0, 0.5 and 1% test levels of DSS). This is considered to be a truly accessory sternebra, and not caused by parental exposure to DSS."

"DSS was administered to Sprague-Dawley rats at levels of 1.0 or 2.0% in the diet on days 6 and 15 of gestation. There were no effects observed at the 1% dose level. However, at 2% DSS produced growth retardation in the dams, significant increase in fetal resorptions, and a significantly higher percentage of externally malformed fetuses. The external anomalies in pups that were derived from DSS treated dams were said to consist primarily of exencephaly of varying degrees of severity, and this malformation was frequently associated with spina bifida and microphthalmia."

"[P]regnant rats which received 2% DSS in the diet from day 6 to day 16 of gestation showed decreased maternal food consumption and weight gain as well as decreased fetal body weights and crown-rump distances compared to control groups. In addition, DSS caused delayed ossification of sternebrae in the foetuses. However, there was no reported incidence of exencephaly at the 2% dose level."

"Three generations of 30 male and 30 female immature Charles River CD Sprague-Dawley rats were fed diets containing 0, 0.1, 0.5 or 1% DSS for 10 and 2 weeks in the parent generation, and at least 10 weeks post weaning in successive generations...There were no effects on the reproductive function of parental animals of either sex during any of the three generations of the study. At the 1% level, body weights were lower than the controls during the premating period of males in all three generations and for F_1 and F_2 females. Body weights for F_1 and F_2 males and females of the 0.5% dose group were slightly lower than controls during the premating period. Pup weights on day 0 of lactation were lower in the treated groups than in the control group, but the difference was significant only for the high dose (1%) group of the third generation. Lower pup weights in the 0.5 and 1% groups resulted in significantly lower pup weights on day 21 for all three generations. Pup survival (91-100%) was comparable between treated and control groups of all generations. The above results indicate that DSS at 0.5% and 1% levels caused a reduction in body weight for parental males of all generations and for F1 and F2 females, and weanling pup weights at these dose levels were lower than the controls in all three generations. However, there were no adverse effects on reproductive function of the test animals nor were there treatment-related microscopic lesions or effects on antemortem function of either sex in any generation."

Inhalation studies

"When rabbits were exposed to an aerosol containing 5% DSS in 95% ethanol and isotonic saline the pulmonary clearance of technetium-99m-labeled diethylenetriamine pentaacetate (99m-Tc-DPTA) from aveoli to blood was accelerated by DSS without affecting gas exchange or lung mechanics."

"[Fixty-six] mongrel dogs were evaluated for the effects of DSS on pulmonary oedema. In the study, DSS was administered as a 1% aerosol in 95% ethanol and isotonic saline. Two hours post treatment the pulmonary extravascular water volume was increased indicating that there was a loss of surfactant activity and an increase in alveolar surface tension."

Human Health Studies

DSS has been used in pharmaceutical products such as stool softener and laxatives for many years. The suggested daily dosage for over-the-counter products containing DSS used for stool softening is 100 to 300 milligrams per day active ingredient for adults, and 100 milligrams per day active ingredient for children 2 to 12 years of age. The 1991 JECFA report notes that

up to 300 mg can be ingested without adverse effects. The following information regarding observations in humans is extracted from that report.

> "Two human subjects were given 200 mg/kg of DSS orally. Peak concentrations in the serum occurred two hours post dosing, and concentrations of DSS found in the plasma of the subjects were similar to those observed in dogs one hour after an oral dose 4 mg/kg.
>
> When patients with T-tube biliary drainage were given doses of 100 mg or 200 mg DSS orally the results of gas chromatography analysis indicated that DSS was present in the bile at concentrations of 2 to 4 x 10^{-5}M.
>
> In a human panel where drugs were prescribed to 6,937 women during the first trimester of pregnancy, 473 received DSS (docusate sodium), and only one gave birth to a child with unspecified congenital disorder."

The HSDB report on DSS notes that this chemical is absorbed from the gastrointestinal tract and is excreted in significant concentrations in bile. In addition, stool softeners containing DSS may increase the intestinal absorption of other drugs when administered concurrently.

Special Considerations for Infants and Children

The toxicity database for DSS includes two oral rat developmental toxicity studies in which effects were observed at the 2% (20,000 mg/kg) dietary level. These effects included exencephaly and decreased fetal body weight and crown-rump length. It should be noted, however, that these effects were observed at very high dose levels.

The Physician Reference Desk (http://www.pdrhealth.com) indicates that over-the-counter stool softeners containing DSS (Brand name Colace) have not been rated by the FDA regarding potential risks to pregnant women. The FDA's system divides drugs into five categories, ranging from completely safe to absolutely forbidden in pregnancy. To qualify for a particular category, a drug must pass (or fail) certain scientific tests in animals, humans, or both. The only recommendation regarding use by pregnant women is to notify their doctor before using this medication. As noted in the 1991 JECFA report, there is limited human data on the effects of this chemical on the developing fetus with one study reporting congenital effects in one case out of 473 participants after exposure to DSS.

Since animal studies indicate effects only at very high dose levels and human data do not provide conclusive evidence of developmental effects, the Agency has determined that at this time there are no definitive data that indicate a potential sensitivity of infants and children. Therefore, the additional tenfold FQPA (Food Quality Protection Act) safety factor has been reduced to 1x.

Hazard Characterization

Acute toxicity data from animal studies indicate low oral and dermal toxicity for DSS. Reproductive toxicity studies, on the other hand, showed effects on lactation and parental body weight and weanling pup weight at 0.5 % DSS in the diet (5,000 mg/kg), but no adverse effects on reproductive function in the test animals were observed at dose levels up to 1% (10,000 mg/kg) in the diet. The JECFA concluded in its 1991 report that "the no-observed-effect level of DSS was 1 g/kg (0.1% or 1,000 mg/kg) in the diet, equivalent to 50 mg per kg of body weight per day". Using a safety factor of 200, a temporary acceptable daily intake (ADI) of 0-0.25 mg per kg of body weight was allocated to DSS, pending the evaluation of results of a long-term study in a rodent species. In 1995, JECFA withdrew its request for the long-term study and increased the safety factor to 500 because of the limited toxicological database on DSS. On the basis of a NOEL of 50 mg/kg of body weight and the new safety factor of 500, JECFA established an ADI of 0-0.1 mg/kg body weight for DSS.

The JECFA also concluded that the inhalation studies with rabbits and dogs did not indicate any adverse pulmonary or systemic effects. No information was provided in the JECFA report regarding the basis for this conclusion. It should be noted that the study summary provided in the JECFA report mentioned increased pulmonary extravascular water volume in the animals tested.

In developmental toxicity studies, ingestion of 2% DSS in the diet caused adverse effects on the fetuses, including exencephaly and increased skeletal abnormalities. The SOCMA report noted that "the effects noted at this concentration [2%] are associated with maternal toxicity as evidenced by growth retardation and a significant increased in fetal resorptions."

V. Exposure Assessment:

Exposure to DSS may occur through FDA-approved uses as food additive, or through its use in products such as stool softeners and laxatives. Short-term use of DSS in pharmaceutical products such as stool softeners can result in exposure of up to 4.28 mg/kg/day, based on a maximum intake of 300 mg active ingredient by a 70-kg person. Consumer intake of DSS from FDA-approved food uses has been estimated to be approximately 0.08 mg/kg body weight per day, while the current ADI established by JECFA is 0 - 0.1 mg/kg for the food additive use of DSS. Use of DSS in pesticide products for agricultural applications and in food-contact sanitizing solutions is expected to result in lower exposure than the FDA direct food additive uses of this compound. Thus, at this time, the Agency has determined that a quantitative risk assessment is not necessary.

VI. Risk Characterization:

DSS exhibits low acute toxicity and is used safely in pharmaceutical products and as a food additive. The studies reviewed in this assessment indicate potential reproductive and

developmental effects from exposure to DSS; however, these effects were observed at very high dose levels.

Uses of DSS are expected to result in human exposure below dose levels that could possibly produce any adverse effects. The current uses of DSS in pharmaceutical products are not likely to pose a risk given the high doses needed to cause acute toxicity. Food additive uses are also not likely to pose a risk since exposure from these uses is expected to be well below the NOEL of 50 mg/kg/day that JECFA determined caused adverse effects in the reproductive tests. As indicated above, exposure from the use of DSS in agricultural pesticide products and food-contact surface sanitizing solutions is expected to be minimal compared to that resulting from the pharmaceutical and food additive uses of DSS.

Taking into consideration all available information on DSS, including its low acute toxicity via oral and dermal routes, its safe uses as food additive and ingredient in pharmaceutical products, and the observation of reproductive and developmental effects only at very high dose levels, the uses of DSS in agricultural pesticide products and in food-contact sanitizing solutions are unlikely to pose a significant hazard to the general public or to any population subgroup.

VII. Environmental Fate/Ecotoxicity/Drinking Water Considerations:

Environmental Fate

According to the HSDB toxicity profile for DSS, this chemical is expected to have low to very high soil mobility based on estimated Koc values ranging from 9.37 to 1041. On the other hand, if released to water, DSS will be essentially nonvolatile based on an estimated Henry's Law constant of 5x10-12 atm-m^3/mol. The HSDB profile indicates that the estimated aqueous base-catalyzed hydrolysis half-lives for this chemical is 243 days at pH of 8 and 6.7 years at pH of 7. In the atmosphere, DSS will exist primarily in the particulate phase. In the vapor phase, it will degrade in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of 18 hrs. Physical removal from air can occur through wet and dry deposition. The HSDB toxicity profile also notes that aquatic bioconcentration is not expected to be an important fate process based on estimated bioconcentration factor (BCF) of 1.13 and experimental BCFs of <0.9 at 0.5 mg/l and <9.3 at 0.05 mg/l, although adsorption to sediment may be possible. Regarding biodegradation, the HSDB profile indicated that several studies have shown that DSS biodegrades rapidly.

Ecotoxicity

Acute toxicity data for fish, aquatic invertebrates and terrestrial plants are presented in Table 5. These data were obtained from published studies summarized in the HPV Test Plan for Sulfosuccinates.

Table 5. Ecotoxicity of Dioctyl Sodium Sulfosuccinate		
Study Type	**Species**	**Results**
Acute Toxicity	Bluegill sunfish	96-hr LC50 = 37 mg/L (Slightly toxic)
	Rainbow trout	96-hr LC50 = 28 mg/L (Slightly toxic)
	Daphnia Magna	48-hr LC50 = 36.2 mg/L
Phytotoxicity	Wandering Jew (Tradescantia bicolor)	24-hr NOEC = 0.625 mmol/L 48-hr NOEC <0.3125 mmol/L

The available data indicates that DSS is slightly toxic to fish. The PBT profiler, on the other hand, estimated that DSS has a chronic fish toxicity value that may cause adverse effects. However, according to the PBT profiler the estimated water solubility of this chemical is not high enough to allow these toxic effects to be expressed (which is referred to as no effect at saturation). Because DSS is not expected to be persistent and bioaccumulative, the PBT profiler notes that this chemical is not expected to concentrate in higher organisms to levels that may be toxic.

VIII. Cumulative Exposure:

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to DSS and any other substances, and DSS does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that dioctyl sodium sulfosuccinate has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. Conclusion:

The current registered uses of butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt have been evaluated and the Agency concludes that there is a reasonable certainty that use of butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt will not pose harm to the general population or to any population subgroup.

X. References:

Chemfinder (www.chemfinder.com), accessed August 2004.

Department of Health & Human Services: Public Health Service: Food and Drug Administration. Agency Response Letter: GRAS Notice No. GRN 000006. December, 1998.

Hazardous Substances Database (HSDB). On-line Scientific Search Engine, National Library of Medicine, National Institute of Health. Http://www.toxnet.nlm.nih.gov. Accessed August 2004. Search term dioctyl sodium sulfosuccinate.

PBT Profiler *(http://www.pbtprofiler.net)* accessed August 2004.

Synthetic Organic Chemical Manufacturers Association (SOCMA) Sulfosuccinates Group. 2001. Test Plan for Sulfosuccinates. HPV Challenge Program: AR201-13787A. Http://www.epa.gov/chemrtk/volchall.htm

World Health Organization (WHO). 1974. Eighteenth Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series, No. 557. FAO Nutrition Meetings Report Series, 1974, No. 54. Http://www.who.int/en

World Health Organization (WHO). 1991. *Toxicological Evaluation of Certain Food Additives and Contaminants (Thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives).* WHO Technical Report Series, No. 806, 1991. Http://www.who.int/en

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