Butylate; CASRN 2008-41-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Butylate

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	10/01/1994
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Butylate
CASRN — 2008-41-5
Primary Synonym — Sutan
Last Revised — 10/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased relative liver weight in male dogs **12-Month Dog Feeding Study** **Stauffer Chemical Co., 1987a**	NOAEL: 5 mg/kg-day LOAEL: 25 mg/kg-day	100	1	5E-2 mg/kg-day

*Conversion Factors and Assumptions — Actual dose tested

I.A.2. Principal and Supporting Studies (Oral RfD)

Stauffer Chemical Company. 1987a. MRID No. 40389101. HED Doc No. 006875. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Beagle dogs (5/sex/dose) were administered gelatin capsules containing 0, 5, 25 or 100 mg/kg-day of butylate. Capsules were administered once per day 1 hour after food was given. Dogs were examined at least twice daily for mortality and clinical signs of toxicity. Detailed physical examinations were performed prior to initiation of the study and weekly thereafter. Body weight data were recorded twice during the pretreatment period, weekly thereafter, and at termination after fasting. Food consumption was reported at pretest and weekly thereafter. Blood was collected at pretest and at 3, 6 and 12 months. All animals that were sacrificed on schedule were subjected to gross pathological examination.

Butylate had no effect on mortality, as all animals survived to termination. No statistically significant effects on body weight were observed. Body weight gain was slightly less for high-dose males and females, but was not reported to be statistically significant. At the high-dose, a

statistically significant ($p<0.01$) increase was observed in platelet count (92 and 91% for males at 6 and 12 months, respectively; 88 and 73% for females at 6 and 12 months, respectively) and alkaline phosphatase (265 and 279% for males at 6 and 12 months, respectively; 200 and 197% for females at 6 and 12 months, respectively) at all time periods examined for both males and females. Other statistically significant changes in hematology and clinical chemistry parameters were not considered to be treatment-related because they were sporadically affected during the study.

Absolute (41%) and relative (56%) liver weights were statistically ($p<0.01$) elevated for high-dose males. Absolute ($p<0.05$, 38%) and relative ($p<0.01$, 48%) liver weights also were statistically elevated for high-dose females. In addition, relative liver weights were statistically ($p<0.05$, 21%) increased in mid-dose males. Thyroid/parathyroid relative ($p<0.01$, 65%) and absolute ($p<0.05$, 49%) organ weights were statistically increased in high-dose males. Microscopically, hepatocellular vacuolation/vesiculation was seen in 2/5 high- dose males. This finding is considered to be treatment-related due to effects observed on liver weights and the increase in alkaline phosphatase observed at this dosage level, since it was not noted in any other group including the controls. Convoluted tubules/brown pigment was reported in the kidneys of 2/5 males and 1/5 females of the high-dose group. The study pathologist considered this effect to be sporadic and not compound-related.

Based increased liver weight in males, the LEL for systemic toxicity is 25 mg/kg-day. The NOEL for systemic toxicity is 5 mg/kg-day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 100 reflects 10 for intraspecies-variability and 10 for interspecies extrapolation.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

1) 12-Month Feeding - dog: Principal study -- see previous description; Core grade minimum (Stauffer Chemical Co., 1987a).

2) 2-Year Feeding - rat: Core grade minimum (Stauffer Chemical Co., 1982).

Groups of Sprague-Dawley CD rats (50/sex/dose) were administered butylate technical via diet for 24 months at dose levels of 0, 50, 100, 200 and 400 mg/kg-day. Food and water were available ad libitum.

No changes were observed in clinical signs, hematology, mortality, clinical chemistries, gross necropsy observations or urinalysis parameters that could be related to compound administration. Male animals that received 200 and 400 mg/kg-day showed a dose-related significant ($p<0.05$) decrease in average body weight as early as the second week that was sustained throughout the remainder of the study. Animals that received 100 mg/kg-day also showed a decrease in average body weight, which was significant ($p<0.05$) on the 78th week of the study and thereafter. The body weights of males receiving 50 mg/kg-day were significantly ($p<0.05$) lower than controls at 104 weeks and at termination of the study, but were not different throughout the major part of the study. Female animals that received dosages of 100, 200 and 400 mg/kg-day showed decreased mean body weights compared with controls, in a consistent, dose- related manner. These differences is mean body weights between control and treated groups were statistically significant as early as the first week of the study and continued to be so throughout the study. The mean body weights of the three highest dose groups at termination were 13, 15 and 18% (males) and 16, 24 and 28% (female) lower than controls. Food consumption was similar among dose groups and controls throughout study. Statistically significant ($p<0.05$) increases were observed in different dose groups at various intervals, but no apparent dose-related trend was observed.

Significant increases also were observed liver-to-body weight ratios in both sexes at various doses and sacrifice intervals. These increases were statistically significant in males at all doses at 24 months; however, these changes alone were not of toxicologic importance since no concomitant significant effects were observed on absolute liver weights and increases in relative liver weights were accompanied by significant decreases in body weights. In addition, analysis of liver-to-brain weight ratios in males at terminal sacrifice indicated that there was no significant increase in the ratio at 50, 100 or 400 mg/kg-day when these values were compared with controls, but a significant increase was observed in males at 200 mg/kg-day (9.36 + or - 1.10) compared with control (8.45 + or - 1.35). It was concluded, therefore, that there were no compound-related effects of toxicologic importance on any organ weights.

Therefore, based on decreased body weight gain, the LEL for systemic toxicity is 100 mg/kg-day. The NOEL for systemic toxicity is 50 mg/kg-day.

3) 2-Generation Reproduction - rat: Core grade minimum (Stauffer Chemical Co., 1986).

Groups of CrlCD (SD)BR rats (25/sex/dose) were administered butylate in the diet over two generations at dose levels of 0, 200, 1000 and 4000 ppm (0, 10, 50 and 200 mg/kg-day).

A statistically significant increase in dehydration was observed in high-dose P0 females (0/25 control, 1/25 low-dose, 0/25 mid-dose, and 6/25 high-dose). Dehydration also was observed in P0 males and P1 males and females but was distributed among the dose-groups in an unrelated

manner. In the first mating of P0 parents, the mean body weights of the high-dose animals were significantly ($p<0.05$) lower than those of the control group for males and females. The same was true for the second mating of this generation. The decreases in body weights were found to be statistically significant ($p<0.05$) when compared with the control group for high-dose P1 males and females for each of the three matings. For mid-dose P1 females, body weights also were significantly ($p<0.05$) depressed during gestation and lactation for each of the three matings. The decrease in food consumption was statistically significant for high-dose P0 males and females at most of the reported time intervals. During gestation and lactation, food consumption also was significantly depressed in the high-dose P0 females. Additionally, the decrease in food consumption was statistically significant for high-dose P1 males and females at most of the reported time intervals. This was also true for the females during gestation and lactation. Food consumption also was significantly depressed in mid-dose males during the following intervals: 14- 23, 84-89, and 217-230/231 days. During gestation and lactation, food consumption was significantly decreased sporadically in mid-dose females. Also, the hematocrit of the high-dose P0 males and females was decreased to a statistically significant extent. Hemoglobin levels also were significantly decreased in high-dose P0 and P1 females. The following statistically significant changes were noted at the high-dose: P0 males: absolute spleen and thymus weights decreased; relative brain, testes, kidney and liver weights were increased; P0 females: relative kidney, brain and liver weights were increased; P1 males: absolute brain and spleen weights were decreased; relative testes weights were increased; P1 females: absolute brain, kidney and thymus weights were decreased; relative brain, heart, spleen and liver weights were increased. Relative liver weights also were increased in mid-dose P0 females. Based on effects observed at the mid- and high-dose, the LEL for systemic toxicity is 1000 ppm (50 mg/kg-day). The NOEL for systemic toxicity is 200 ppm (10 mg/kg-day).

A statistically significant ($p<0.05$) decrease in mean pup weights at various time intervals was found when compared with the control group for the high-dose group of each generation and mating, and for the mid-dose group for the F2a generation. A total born (litter size) decrease was found to be statistically significant ($p<0.05$) when compared with the control group for the F1a, F2a and F2b generations at the highest dose tested. A few small pups were noted in the high-dose group. The following statistically significant differences in organ weights were considered to be treatment-related: in the high-dose, decreased absolute kidney and brain weights of F1b males and females and kidney weights of F2c males and increased relative liver weights of males and females of the F2c generation; in the mid-dose, decreased absolute brain weight in the F1b males. Based on the effects observed at the mid- and high- dose levels, the LEL for reproductive toxicity is 1000 ppm (50 mg/kg-day). The NOEL for reproductive toxicity is 200 ppm (10 mg/kg-day).

In F1b pups a treatment-related increase was observed in the incidence of retinal folds and dilated kidneys (renal pelvis) by both the number of pups (20/119) affected and by litter (10/19)

at the highest dose tested. An increase in these lesions was not observed in any other generation nor in the rat developmental toxicity study (Stauffer Chemical Co., 1983). Based on the above effects, the LEL for developmental toxicity is 4000 ppm (200 mg/kg-day). The NOEL developmental toxicity is 1000 ppm (50 mg/kg-day).

4) Developmental Toxicity - rat: Core grade minimum (Stauffer Chemical Co., 1983).

Groups of pregnant Sprague-Dawley CD rats were administered 0, 40, 400 or 1000 mg/kg-day of butylate daily by oral intubation on each of gestation days 6 through 20. All animals were dosed at a volume of 5 ml/kg, based on the female's body weight at day 6 of gestation. The control, low- and mid-dose groups were comprised of 26 females each, while the high-dose group consisted of 28 females.

Maternal toxicity was noted in high-dose animals, as evidenced by inactivity and excessive salivation. A significant increase in the incidence of salivation also was observed in mid-dose animals. Three (11.1%) high-dose animals died, apparently of compound-related toxicity, and a fourth died of spinal trauma incurred during dosing. Body weights were significantly ($p<0.05$) decreased in the mid- and high-dose groups, but not in the low-dose group. Similar results were observed when data on weight change during the treatment period were analyzed. Food consumption was significantly ($p<0.05$) reduced throughout the dosing period for high-dose dams, and during most of this period for the mid-dose group, while low-dose rats were unaffected in terms of food intake. Based on the effects observed at the mid-dose level, the LEL for maternal toxicity is 400 mg/kg-day. The NOEL for maternal toxicity is 40 mg/kg-day.

No increased incidences of either gross external soft tissue or skeletal malformations were reported, indicating a lack of teratogenicity. Signs of prenatal toxicity were observed, however and, among others, included decreased mean fetal body weights and an increased incidence of misaligned sternebrae observed at the mid- and high-dose levels. The percentages of affected litters with misaligned sternebrae for the mid- (40.9%) and high- (37.4%) dose groups were outside the historical range (29.2%). This was also true for the percentage of affected fetuses, with 7.79 and 10.34% for the mid- and high- dose groups, respectively, versus a high of 4.1% for the historical controls. In addition, the incidence of incomplete ossification of at least one of the first through fourth sternebrae was significantly ($p<0.05$) increased at the high-dose level; the percentages for affected litters (29.4%) and fetuses (9.48%) were outside the historical control ranges (16.0 and 3.7%, respectively). Based on the effects noted above, the NOEL and LEL for fetotoxicity are 40 and 400 mg/kg-day, respectively.

Two high-dose females completely resorbed their litters. From the description of the uterine contents, it appeared that resorption occurred shortly after dosing commenced. The increase incidence of resorptions at the high-dose level was not statistically significant because the

increase was entirely due to the contribution of the two totally resorbed litters; however, fetal body weights were significantly decreased in the mid- and high-dose groups. Based on the increase in early resorptions, the NOEL and LEL for embyrotoxicity are 400 and 1000 mg/kg-day, respectively.

5) Developmental Toxicity - rabbit: Core grade minimum (Stauffer Chemical Co., 1987b).

Groups of pregnant New Zealand White rabbits (16/group) were administered 0, 10, 100 and 500 mg/kg-day of butylate by oral intubation from gestation day 7 through 19.

Although no significant differences in mean body weight of pregnant does were recorded on any individual sampling day during the treated (or post-treated) portions of gestation, a significant ($p<0.05$) decreased body weight gain was found for the treated interval days 7 through 13 at the 500 mg/kg-day dose level. Mean feed intakes of the high-dose group were significantly ($p<0.05$) decreased during treatment (as measured on gestation days 10, 13 and 19), but apparently recovered during the post-treatment period. Both mean absolute and relative ovarian weights were significantly ($p<0.05$) increased among high-dose animals. Indication of a dose-relationship was suggested by the slight (but insignificant) increase at the 100 mg/kg-day level. Based on the effects observed at the highest dose tested, the LEL for maternal toxicity is 500 mg/kg-day. The NOEL for maternal toxicity is 100 mg/kg-day. Developmental toxicity was not observed at any tested dose. Therefore the NOEL for developmental toxicity is equal to or greater than 500 mg/kg-day.

6) Developmental Toxicity - mice: Core grade supplementary (Stauffer Chemical Co., 1967a).

Groups of Charles River mice were administered 0, 4, 8 and 24 mg/kg-day of butylate in the diet from day 6 of post-vaginal plug formation (day zero) until termination of gestation (days 17.5 - 19.5). The control and mid-dose groups were comprised of 40 animals each, while the low- and high-dose groups consisted of 20 animals each. No evidence of maternal or developmental toxicity was observed at any of the doses tested. Therefore, the NOEL for maternal and developmental toxicity are equal to or greater than 24 mg/kg-day.

Other Data Reviewed:

7) 2-Year Feeding - mouse: Core grade minimum (Stauffer Chemical Co., 1979).

Groups of CD-1 mice (60/sex/dose) were administered 0, 20, 80 and 320 mg/kg- day of butylate in diet for 24 months. Female body weights were statistically decreased at the mid- and high-dose levels. A decrease was observed in both relative and absolute kidney weights for high-dose males and females. Liver findings (cellular infiltrates and focal necrosis) were higher in

incidence for the high-dose groups of both sexes when compared with controls. Kidney findings (amyloidosis, chronic nephritis, and lymphocytic foci) were slightly higher in high-dose males, and higher in both mid- and high-dose females when compared with controls. Based on the dose-related effect observed seen in the liver and kidney, the LEL for systemic toxicity is 80 mg/kg-day. The NOEL for systemic toxicity is 20 mg/kg-day.

8) 1-Year Feeding - rat: Core grade supplementary (Stauffer Chemical Co., 1978).

Groups of Sprague-Dawley rats (60/sex/dose) were administered 0, 10, 30 and 90 mg/kg-day of butylate orally for 56 weeks. The control group received the vehicle corn oil at 1%, by weight of diet. At 15 weeks, the dosing regimen for 10 animals of the high-dose group was changed to 180 mg/kg-day.

Body weights were decreased in males at doses of 30, 90 and 180 mg/kg-day during the early growth period (-1 to 17 weeks) and then again toward the end of the test (44-55 weeks). Females were also affected but at the two highest doses. There were equivocal suggestions of increases in some absolute organ weight values; for example, liver weights of the 90 and 180 mg/kg-day animals (at Week 47: 18 and 16% for males and 5 and 8% for females, respectively) and testes (2 and 3%). Statistically significant ($p<0.05$) increases in relative organ weights were observed in the high-dose males sacrificed at Week 47 (20%), the heart of high-dose males sacrificed at termination (12%) and the testes of mid- and high-dose males sacrificed at termination (16 and 32%, respectively). Blood clotting parameters were reported to be affected but only at 10 mg/kg-day, and additional organ changes (liver bile duct inflammation; focal hemorrhages in testes and uteri; increased chronic myocarditis, especially in males) were reported at the highest dose tested.

Although useful information was provided, this study is considered core grade supplementary because no histopathology was performed on low- or mid-dose groups, hence no final NOEL and LEL for systemic toxicity could be established.

9) 13-Week Feeding - dog: Core grade supplementary (Stauffer Chemical Co., 1967b).

Groups of beagle dogs (4/sex for control group, 3/sex for treated groups) were administered 0, 450, 900 and 1800 ppm (0, 11.25, 22.5 and 45 mg/kg-day) of butylate in the diet for 13 weeks. No effects were apparent on behavior or body weights; or neurological, ophthalmological or hematological functions or on blood chemistries, brain ChE or gross organ appearances or weight. Also no deaths were observed in any of the animals. Both gross and microscopic necropsy findings were comparable.

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The principal study was well conducted and considered acceptable to satisfy the minimum criteria for chronic testing in a nonrodent. Therefore, the study is given a high confidence rating. High confidence is given to the butylate database since adequate studies for chronic feeding toxicity in a second species, developmental, and reproductive studies exist. Additionally, a number of the supportive studies report liver weight increases, which support the effects observed in the principal study. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 11/21/1985, 02/26/1986, 04/22/1986, 03/18/1987, 05/25/1988, 01/18/1989, 12/14/1993

Verification Date — 12/14/1993

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Butylate conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Butylate
CASRN — 2008-41-5
Primary Synonym — Sutan

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Butylate
CASRN — 2008-41-5
Primary Synonym — Sutan

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Butylate
CASRN — 2008-41-5
Primary Synonym — Sutan

VI.A. Oral RfD References

Stauffer Chemical Company. 1967a. MRID No. 00129544. HED Doc. No. 003070. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Stauffer Chemical Company. 1967b. MRID No. 00026314. HED Doc. No. 003070. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Stauffer Chemical Company. 1978. MRID No. 00035843. HED Doc. No. 003070. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Stauffer Chemical Company. 1979. MRID No. 00035844. HED Doc. No. 003070, 003830. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

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Stauffer Chemical Company. 1983. MRID No. 00131032. HED Doc. No. 004338, 006875. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Stauffer Chemical Company. 1986. MRID No. 00160548, 00155519. HED Doc. No. 005962, 006875. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Stauffer Chemical Company. 1987a. MRID No. 40389101. HED Doc. No. 006875. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Stauffer Chemical Company. 1987b. MRID No. 40389102. HED Doc. No. 006875. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Butylate
CASRN — 2008-41-5
Primary Synonym — Sutan

Date	Section	Description
06/30/1988	I.A.	Withdrawn; new RfD verified (in preparation)
08/22/1988	I.A.	Revised Oral RfD summary added
02/01/1989	I.A.	Withdrawn; new RfD verified (in preparation)
03/01/1989	I.A.	Revised Oral RfD summary added
10/01/1994	I.A.	Oral RfD summary replaced with revised summary
10/28/2003	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Butylate
CASRN — 2008-41-5
Primary Synonym — Sutan
Last Revised — 09/30/1987

- 2008-41-5
- BIS(2-METHYLPROPYL)CARBAMOTHIOIC ACID S-ETHYL ESTER
- BUTILATE
- Butylate
- CARBAMIC ACID, DIISOBUTYLTHIO-, S-ETHYL ESTER

- CARBAMOTHIOIC ACID, BIS(2-METHYLPROPYL)-, S-ETHYL ESTER
- DIISOBUTYLTHIOCARBAMIC ACID S-ETHYL ESTER
- DIISOCARB
- ETHYL N,N-DIISOBUTYLTHIOCARBAMATE
- ETHYL-N,N-DIISOBUTYL THIOLCARBAMATE
- R-1910
- S-ETHYL BIS(2-METHYLPROPYL)CARBAMOTHIOATE
- S-ETHYLDIISOBUTYL THIOCARBAMATE
- S-ETHYL N,N-DIISOBUTYLTHIOCARBAMATE
- STAUFFER R-1910
- Sutan