NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

1,2,3,4-BUTANETETRACARBOXYLIC ACID

CAS Number 1703-58-8

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Submitted to:
NATIONAL TOXICOLOGY PROGRAM

Submitted by:
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OVERVIEW[1]

Nomination History: *1,2,3,4-Butanetetracarboxylic acid (BTCA) was nominated for carcinogenicity testing with a moderate to high priority by the National Cancer Institute (NCI) in November, 1989. This compound was nominated because of the increased potential for its use as a substitute for formaldehyde in the permanent press treatment of cotton resulting from the lowering of the TLV for formaldehyde. The NCI also noted that there are limited toxicity studies on this compound. These studies do not include data concerning the chronic toxicity or carcinogenicity of this compound. The nomination of BTCA was brought to the attention of the NCI in 1988 by the National Cotton Council of America and the U.S. Department of Agriculture.*

Chemical and Physical Properties: *BTCA is an off-white powder with a melting range of 196-237°C (385-458°F). This compound is soluble in water and alcohol, incompatible with strong oxidizing agents, and unstable in the presence of excessive heat and light. Decomposition of this compound results in toxic fumes of carbon dioxide and carbon monoxide.*

Production/Uses/Exposure: *The production volume of BTCA was reported in the public file of the EPA Toxic Substances Control Act (TSCA) Inventory by three manufacturers to range from 2,000-21,000 pounds. This compound is not listed in the U.S. International Trade Commission's publication, Synthetic Organic Chemicals or in SRI's Chemical Economics Handbook. BTCA has been patented for use as a formaldehyde substitute to introduce durable ester cross-links into cotton cellulosic textiles in a treatment that enhances the fabric's crease and shrinkage resistance and improves its durability and performance. BTCA has also been patented for use as a heat resistant corrosion inhibitor, a component of a lubricating oil, and a starting material used to produce a*

polyimide adhesive. BTCA is used as an ingredient in epoxy and alkyl resin systems and as a component of polyimide ultrafiltration membranes. BTCA is not listed in the National Occupational Exposure Survey conducted by NIOSH. OSHA has not established a permissible exposure limit, NIOSH has not recommended an exposure limit, and ACGIH has not recommended a threshold limit value.

Toxicological Effects:

Human: *No data were found concerning the chemical disposition, acute, prechronic, chronic/carcinogenic, reproductive or teratogenic effects of BTCA in humans.*

Animal: *An oral rat LD50 of 1.72 g/kg and a dermal rabbit LD_{50} of >8.00 g/kg have been reported for BTCA. This chemical, tested at a concentration of 8.19 mg/L, was not found to induce inhalation toxicity in rats following a one hour exposure. Application of BTCA to the conjunctival sac of the rabbit eye caused severe and corrosive irritation and permanent ocular damage. 1,2,3,4-Butanetetracarboxylic acid was not found to be a primary skin irritant (irritation index = 0.9) following dermal application to rabbits. No data were found on the chemical disposition, prechronic, chronic/carcinogenic, teratogenic or reproductive effects of BTCA in animals.*

Genetic Toxicology: *No data were found on the genetic toxicology of BTCA in prokaryotic or eukaryotic organisms.*

Structure Activity Relationships: *No data were found on the structure activity relationships of BTCA.*

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[1] The information contained in this Executive Summary of Safety and Toxicity Information (ESSTI) is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

I. NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute [NCI, 1989a,b]
2. Date: November, 1989
3. Recommendations: Carcinogenicity
4. Priority: Moderate to high
5. Rationale/Remarks:
    - Increased potential for use as a formaldehyde substitute in the permanent press treatment of cotton resulting from the lowering of formaldehyde's TLV
    - Increased importation and/or initiation of domestic production due to:
        - refinements in processing and improved cost effectiveness
        - lack of suitable alternatives for use in textile finishing
        - opening up of new applications markets
    - Limited toxicity studies
    - Lack of carcinogenicity data
    - Nomination brought to the attention of the NCI in 1988 by the National Cotton Council of America and the U.S. Department of Agriculture because of interest in the use of this compound to treat cotton

B. Chemical Evaluation Committee Review

1. Date of Review: August 8, 1991
2. Recommendation:
    - Toxicity
    - Reproductive and developmental effects studies
3. Priority: High
4. NTP Chemical Selection Principle(s): 2, 8
5. Rationale/Remarks:
    - High production
    - Potential for human exposure
    - Potential substitute for formaldehyde
    - Lack of toxicity data

C. Board of Scientific Counselors Review

1. Date of Review:

2. Recommendations:

3. Priority:

4. Rationale/Remarks:

D. Executive Committee Review

1. Date of Review:

2. Decision:

II. CHEMICAL AND PHYSICAL DATA

A. Chemical Identifiers

CAS No. 1703-58-8
RTECS No. EK6100000
Molecular formula: $C_8H_{10}0_8$
Molecular weight:234.16

B. Synonyms and Trade Names

Synonyms: 1,2,3,4-butanetetracarboxylic acid (8CI and 9CI);
butanetetracarboxylic acid;
tetracarboxybutane;
meso-butane-1,2,3,4-tetracarboxylic acid

Trade Names: No data were found.

C. Chemical and Physical Properties

Description:	Off-white powder [Lenga, 1988]. White leaf crystals [Weast, 1989].
Melting Point:	196°C (385°F) Aldrich, 1990; Lenga, 1988] 236-237°C (457-458°F) [Weast, 1989].
Boiling Point:	No data were found.
Density/Specific Gravity:	No data were found.
Refractive Index:	No data were found.
Solubility in Water:	Soluble [American Tokyo Kasei, Inc., 1986; Weast, 1989].
Solubility in other Solvents:	Soluble in ethyl alcohol [Weast, 1989]. Very soluble in ethanol; slighly soluble in ether and chloroform; insoluble in benzene and ligroin [Grasselli and Richey, 1975].
Log Octanol/Water Partition Coefficient:	No data were found.
Reactive Chemical Hazards:	Unstable in the presence of excessive light and heat [American Tokyo Kasei, Inc., 1986]. Incompatible with strong oxidizing agents. Decomposition products include carbon dioxide and carbon monoxide [Lenga, 1988].
Flammability Hazards:	No data were found.

III. PRODUCTION/USE

A. Production

1. Manufacturing Process

A standard method for the production of BTCA is nitric acid oxidation of the corresponding cycloalkene dicarboxylic acid in the presence of a suitable catalyst. A method reported by Franz *et al.* involves the reaction of 4,5-dihydroxyhexahydrophthalic acid with nitric acid in the presence of a vanadium catalyst (such as ammonium metavanadate) to achieve a 90% yield of BTCA. When 4-keto-5-nitrato-1,2-cyclohexanedicarboxylic acid was used as the starting compound, a 95% yield of BTCA was obtained. Also in this study, *cis*- D^4 tetrahydrophthalic acid was reacted, using this procedure, to produce 75% *meso*-BTCA. The same reaction carried out with the corresponding tetrahydrophthalic anhydride as the starting material yielded only 60-65% *meso*-BTCA. In the absence of a vanadium catalyst, yields of BTCA were negligible [Franz *et al.*, 1965].

In another study, industrial production of BTCA was accomplished by oxidizing tetrahydrophthalic anhydride (a Diels-Adler reaction product of maleic anhydride and butadiene), with nitric acid in the presence of an ammonium metavanadate catalyst. This process, however, resulted in toxic gases and nitro by-products that had to be treated. The process was modified to eliminate the formation of by-products and the need for equipment to prevent the discharge of nitrous oxides. To more efficiently produce BTCA, tetrahydrophthalic anhydride was subject to oxidative cleavage using hydrogen peroxide in the presence of at least one catalyst. Catalysts selected included tungstic acid, molybdic acid, and several heteropoly acids of tungstic and molybdic acids. The authors report that this process provided high yields (75-85%) of BTCA with high purity [Nakazawa and Fujitani, 1986].

BTCA has also been prepared by passing ozone through an aqueous alkaline emulsion of 4-cyclohexene-1,2-dicarboxylic anhydride, hydrogen peroxide, and sodium hydroxide at a temperature between 5°C and 15°C. No yields were reported [Fremery and Fields, 1966]. To make this procedure more efficient and economical, a Japanese company produced BTCA in high yield using less hydrogen peroxide. The optimum process involved oxidizing tetrahydrophthalic acid or its anhydride in acetic acid at a temperature between 0°C and 75°C with an ozone-containing gas (oxygen). This ozonide was oxidized further with molecular oxygen-containing gas (oxygen, air) at 90-120°C to obtain an oxidation product mixture, which was heated in the presence of 60% hydrogen peroxide to produce BTCA in approximately 80-85% yields [Tate *et al.*, 1979].

2. Producers and Importers

U.S. Producers:

Producers[2]

Producers	**Reference**
Ortec, Incorporated Easley, South Carolina	Ortec, 1991
Schweizerhall Corporation (formerly Chemical Dynamics Corporation) Plainfield, New Jersey	OPD, 1988; Schweizerhall, 1991
European Producers:	
Chemie Linz Ges. mbH Linz, Austria	SRI, 1990
Gelsenberg Chemie West Germany	F & S Indexes, 1991
Mitsui Toatsu Chemicals Tokyo, Japan	F & S Indexes, 1991
Tokyo Kasei Kogyo Company Tokyo, Japan	American Tokyo Kasei, Inc., 1991

Importers:

Importers	**Reference**
American Tokyo Kasei, Incorporated	

Portland, Oregon	American Tokyo Kasei, Inc., 1991
Danzas New York, New York	Piers Imports, 1991
Permacell America Roselle, Illinois (formerly Nitto Denko America, Incorporated, Lake Success, New York)	USEPA, 1991

3. Volume

The production volume of BTCA is reported in the public file of the EPA Toxic Substances Control Act (TSCA) Inventory. In 1983, four manufacturers were listed as producers of this chemical. Three manufacturers listed a total production volume ranging from 2,000-21,000 pounds, while one manufacturer reported a zero production volume for BTCA [USEPA, 1991].

BTCA is not listed in the United States International Trade Commission's publication Synthetic Organic Chemicals for the years 1984-1988 [USITC, 1985-1989]. BTCA is not listed in SRI's Chemical Economics Handbook [SRI, 1991].

A representative of Ortec, Incorporated, reported that this company produces approximately 3 million pounds of BTCA annually for distribution to the textile industry. He also stated that Ortec manufactures and distributes this chemical for other industries at various purities, but he was unable to provide production volumes [Ortec, 1991].

A representative from Schweizerhall Chemical Company (formerly Chemical Dynamics Corporation) reported little or no production volume for BTCA for the past three years. She stated that only very small research quantities have been manufactured by this company [Schweizerhall, 1991].

The Cotton Council anticipates that refinements in the processing and application of BTCA, along with the improved cost effectiveness of manufacturing procedures, will lead to the chemical's increased importation and/or initiation of domestic production. The demand for BTCA, should it replace formaldehyde-containing compounds, could be 50 million or more pounds for finishing textile apparel [NCI, 1989b]. A representative from the U.S. Department of Agriculture believes that this is a conservative estimate [USDA, 1991].

4. Technical Product Composition

BTCA is available at 99% purity from Aldrich Chemical Company [Aldrich, 1990] and American Tokyo Kasei, Inc. [American Tokyo Kasei, Inc., 1986]. No other data concerning the composition of commercial forms of this compound were available.

B. Uses:

The commercial use of BTCA as a cross-linking agent (6.3% by weight of treating solution) in a pad-dry-cure process for introducing durable ester crosslinks into cotton cellulosic textiles is currently being explored. The recently patented technology produces a formaldehyde-free, odorless treatment that enhances fabric crease and shrinkage resistance, improves durability and performance, and imparts thermal recurability and soil release properties [Welch and Andrews, 1988; Welch and Andrews, 1989]. By eliminating formaldehyde and the release of formaldehyde vapors, the process also is safer for textile workers and consumers [Welch and Andrews, 1989; Chicago Tribune, 1991].

Although the technology is well-known to the textile industry, commercial use of BTCA for this application is, to date, insignificant [USDA, 1991]. Reasons for this include the high cost of BTCA ($40/pound vs. 40¢/pound for formaldehyde) [PTS, 1991], the high cost required for a commercial plant to begin using the procedure ($20-30 million), and the reported recent decline in pressure from OSHA and the EPA to employ a formaldehyde substitute [USDA, 1991]. Only one American plant (Ortec, Inc.) was found to be conducting pilot experiments using BTCA in a non-formaldehyde finishing system [Trade and Industry ASAP, 1991]. According to the U.S. Department of Agriculture, Glotex Chemicals (supplied by Ortec) is considering licensing the technology [USDA, 1991] and, if the cost can be reduced, the procedure may become the industry standard [Chicago Tribune, 1991].

Other Uses:

- Curing agent for use in epoxy resin systems [Kirk-Othmer, 1980; Sax and Lewis, 1987].
- Component of alkyd resins [Sax and Lewis, 1987] used in plastics, paint vehicles, and decorative coatings [Budavari, 1989].
- Starting material used with polyamines (*i.e.*, methylene dianiline) to produce water soluble polyimide resins for electric wire coatings, films, composite matrices, adhesives [Pike, 1984], and ultrafiltration membranes [Iwama and Kazuse, 1982].

Other Patented Uses: (obtained from patents issued between 1985 and 1991)

- Component (15%) of an aqueous solution with sodium hydroxide for use as a lubricating oil for forging [Fujino *et al.*, 1990].
- Heat-resistant corrosion inhibitor for copper and copper alloys [Maeda, 1987].
- Starting material in the production of BTCA dianhydride, which is used with a diamine to produce a flexible, flame- resistant, polyimide adhesive [Gagliano and Long, 1987].

IV. EXPOSURE/REGULATORY STATUS

A. Consumer Exposure

No quantitative data were found on consumer exposure to BTCA. Due to the potential future use of this compound as a formaldehyde substitute in the treatment of cotton and cotton blend fabrics [Welch and Andrews, 1988], the potential for consumer exposure may exist. However, there is no current evidence that consumers are exposed to residual amounts of this chemical through contact with treated textiles [NCI, 1989b].

B. Occupational Exposure

No data were available from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, concerning occupational exposure to BTCA [NIOSH, 1991].

Currently workers involved in the production of BTCA at chemical manufacturing plants are exposed to this compound. Workers in textile treating plants using BTCA, may potentially be exposed to this chemical pending its commercial use.

The potential for occupational exposure also exists from the use of this compound in the production of alkyd resins and in the curing of epoxy resins [Sax and Lewis, 1987]. Alkyd resins are used in the production of paint vehicles, plastics, and decorative coatings [Budavari, 1989], while epoxy resins are used in adhesives, laminating and molding compounds, surface coatings, and reinforced plastics [Plunkett, 1987].

C. Environmental Occurrence

No data were found.

D. Regulatory Status

OSHA has not established a permissible exposure limit (PEL).

E. Exposure Recommendations

- ACGIH has not recommended an exposure limit (TLV).

- NIOSH has not recommended an exposure limit (REL).

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[2]In addition to the producers listed in this summary, U.S. EPA TSCA inventory also lists Chemical Processing, Essex Group (Fort Wayne, Indiana), Organic Chemicals, Inc. (Grandville, Michigan), Nitto Denko Amerida, Inc. (Lake Success, New York), and Mallinchrodt, Inc. (St. Louis, Missouri) as producers of BTCA [USEPA, 1991]. Personal communications with these companies, however, indicate that this information is now inaccurate. Mallinckrodt no longer produces BTCA [Mallinchrodt, 1991], the Chemical Processing Department of Essex Group also does not produce the compound [Essex Group, 1991], and Organic Chemicals is going out of business [Organic Chemicals, 1991]. Nitto Denko was bought by Permacell America, and adhesive coatings company which is located in Roselle, Illinois Permacell does not produce any chemicals on-site [Permacell, 1991].

V. TOXICOLOGICAL EFFECTS

A. Chemical Disposition

1. Human Data

No data were found.

2. Animal Data

No data were found.

B. Acute

1. Human Data

No data were found.

2. Animal Data

oral, rat

Male and female albino COX-SD rats were used to evaluate the acute oral toxicity (LD_{50}) of BTCA when administered as a single dose. Groups of ten rats (5 males and 5 females) were given 0.80, 1.26, 1.59, 2.00, or 3.17 g/kg of the test material administered as a 10% w/w solution in deionized water. The animals were observed daily for 14 days for any gross signs of systemic toxicity and surviving animals were weighed on day 7 post-treatment. Each animal that succumbed (n=21) was weighed and necropsied at the time of death, and surviving animals (n=29) were weighed, sacrificed, and necropsied at the end of the observation period (day 14).

The LD_{50} values for the group of ten rats and for male and female rats are presented in Table 1 below. All animals at the two highest doses (2.00 and 3.17 g/kg) exhibited gross signs of 1,2,3,4-butanetetracarboxylic acid-induced toxicity, and 20/30 animals showed signs of toxicity at the three lowest dose levels (0.80, 1.26, and 1.59 g/kg). At the 0.80 g/kg and 1.26 g/kg dose levels, animals had pronounced or severe diarrhea less than 24 hours after dosing (4/10 and 7/10, respectively). Animals treated with 1.59 g/kg BTCA exhibited hypoactivity (3/10), diarrhea (9/10), piloerection (1/10), and malaise (3/10) within 24 or 48 hours of dosing. When treated with 2.00 g/kg of the test compound, animals exhibited hypoactivity (10/10), hypersalivation (1/10), diarrhea (4/10), unkempt pelage (2/10), piloerection (2/10), malaise (9/10), and proneness (3/10) within 24 or 48 hours. Toxicological signs seen in animals in the highest dose group (3.17 g/kg) in less than 24 hours included hypoactivity (10/10), hypersalivation (2/10), malaise (7/10), and proneness (10/10). Surviving animals returned to normal within 24 and 96 hours following treatment. Body weights of surviving animals remained constant or showed a slight decrease (0.0 to -9.0 g) in four animals seven days after treatment, and a slight decrease (-3.4%) in one animal fourteen days after treatment. All other survivors showed normal gains. Animals that succumbed during the experiment (n=25) exhibited weight losses (-1.0 to -13.1%) at the time of death, with the exception of two animals that showed essentially constant weights (+0.8 and +2.6% %).

Necropsy of animals that succumbed during the fourteen day observation period revealed several abnormalities. In the 1.26 g/kg and 1.59 g/kg dose groups, animals that died (1 and 2 animals, respectively) had moderate to severe congestion of the adrenals, kidneys, liver, and lungs, and erosion and blanching of the stomach mucosa. The animal in the 1.26 g/kg dose group also had moderate congestion of the intestines, and severe blanching of the small intestine. All of the 8 animals in the 2.00 g/kg dose group that succumbed during the study exhibited moderate to severe congestion of the adrenals, kidneys, liver, and lungs, and erosion of the stomach mucosa. Other abnormalities seen in these animals included moderate congestion of the intestines (4/8), brownish-gray coloration of the lungs (1/8), severe blanching of the small intestine (5/8), blanching of the stomach mucosa (7/8), and lesions on the stomach mucosa (1/8). All animals treated with 3.17 g/kg BTCA expired during the study and all 10 exhibited moderate to severe congestion of the adrenals, kidneys, liver, and lungs, and blanching and erosion of the stomach mucosa. Other abnormalities seen in this group included moderate congestion of the intestines (6/10), a paleness of the liver (2/10), a brownish-gray coloration of the lungs (1/10), and blanching of the small intestine (9/10). Necropsy of surviving animals showed no abnormalities, with the exception of three rats that exhibited a hollowing of the renal pelvises.

The investigators of this study concluded that 1,2,3,4-butanetetracarboxylic acid can be classified as moderately toxic by oral administration [Scientific Associates, Inc., 1980a].

Table 1: Acute Toxicity of 1,2,3,4-Butanetetracarboxylic Acid

Route	Species/Strain	# of Animals (sex)	Dose (g/kg)	Confidence interval (g/kg)	Reference
Oral	rat/COX-SD	10/(either sex)	LD_{50} 1.72	(1.42 - 2.08)	Scientific Associates, Inc., 1980a
Oral	rat/COX-SD	5 (male)	LD_{50} 1.74	(1.33-2.28)	Scientific Associates, Inc., 1980a
Oral	rat/COX-SD	5 (female)	LD_{50} 1.62	not done*	Scientific Associates, Inc., 1980a

*No statistical analysis was done for this group since mortality between 0 and 100% was observed only in one of the five dose levels.

inhalation, rats

Ten (five males, five females) albino rats of the COX-SD strain were used to evaluate the acute inhalation toxicity produced by an undiluted powder of BTCA introduced to the animals in a dust form. The duster delivered a total of 1.7 grams of the substance into a 57- liter glass chamber at a flow concentration of 8.19 mg of test material per liter of air, at a flow rate of 2.5 liters per minute for a period of 60 minutes (plus a 23 minute equilibration period). The animals were observed for gross effects during the exposure period and daily for the next fourteen days. Body weights were recorded seven days after exposure. Following the 14-day observation period, all animals were weighed, sacrificed, and necropsied.

All animals survived the exposure period and subsequent 14-day observation period. No gross toxicological effects were seen in any animal during the test period. Body weights recorded at day seven and day fourteen did not show any abnormalities; the animals showed weight gains within the expected limits. Finally, necropsy of the animals showed a moderate congestion of the lungs in three of the ten animals and slightly mottled lungs in three other animals. The authors reported that it is not possible to attribute the lung congestion observed in these animals to treatment with BTCA, since this type of congestion is often observed as a sacrifice artifact in rats. No other abnormalities were found in the remaining animals. At this ambient concentration (8.19 mg/liter), BTCA was not found to exhibit inhalation toxicity in rats [Scientific Associates, Inc., 1980b].

dermal, rabbits

Twelve New Zealand Albino rabbits (six males and six females) were used to evaluate the potential dermal toxicity of BTCA following a single 24-hour exposure. The concentrations for dermal application were 2.0 g/kg (n=4), 4.0 g/kg (n=4), and 8.0 g/kg (n=4), each as a 50% w/w suspension in isotonic saline. Prior to exposure, animals were prepared by clipping the skin of the trunk free of hair. One-half of the animals in each group (n=2) were further prepared by making epidermal abrasions over the area of exposure sufficiently deep enough to penetrate the stratum corneum, but not to disturb the derma. The test suspensions of BTCA were administered under binders fastened to each animal for a period of 24 hours. After 24 hours, the binders were removed, the amount of unabsorbed material was estimated, and the remaining suspension was wiped from the skin. The animals were observed for gross effects at regular intervals on the day of dosing and daily for 14 days, and any animals that perished were necropsied. When the observation period was completed, all surviving animals were weighed, sacrificed, and necropsied.

Death occurred only in animals treated with 8.00 g/kg of 1,2,3,4-butanetetracarboxylic acid (1/4 rabbits). Due to the volume of material required to produce this dose level (35-45 ml), it was concluded that this was the highest dose practicable to administer. Consequently, the acute LD_{50} of BTCA, when applied as a 50% w/w suspension in isotonic saline to the skin of the rabbits, was determined to be greater than 8.00 g/kg. At all dose levels, the rabbits exhibited moderate to severe erythema with chemical burns and/or blanching, especially along the

abrasions. The intensity of the reactions increased with the dose level. On days 7 and 14, desquamation and drying were also observed. At each dose level, the signs of systemic toxicity were limited. At the highest level (8.00 g/kg body weight), one animal exhibited generalized weakness for 72 hours, and three animals were observed to be thin after 72 hours and until day 10 of the study. Wry neck was seen in two animals at the 2.00 g/kg body weight dose level. Two animals in this dose group also exhibited a generalized weakness for 24-48 hours. No other signs of systemic toxicity were observed.

From gross necropsy of animals that succumbed, the skin was observed to have severe erythema of the sides and ventrum with severe congestion of the subcutaneous tissue. The stomachs were blanched with severe erosion of the mucosal surface, and the small intestines showed severe scattered congestion. No other abnormalities were observed. Gross necropsy of the animals sacrificed at day 14 showed no remarkable abnormalities, with the exception of one animal treated with 8.00 g/kg BTCA that showed an approximate 90% loss of fat tissue. Final body weight data of surviving animals at day 14 revealed that three animals (two with intact skin, one with abraded skin) in the 2.00 g/kg dose group had significant (10% or greater) weight gains. At 4.00 g/kg, one (abraded skin) had a significant weight gain. Other surviving animals had weight gains or losses that were less than 10%. The authors reported that as the term is defined in the Federal Hazardous Substances Act (FHSA), BTCA was not found to be a toxic substance following dermal application to rabbits [Scientific Associates, Inc., 1980c].

dermal, rabbits
Six New Zealand White rabbits of either sex were used to determine the type and extent of dermal reaction resulting from topical application of BTCA as a 50% w/v suspension in isotonic saline. Prior to application, the back of each animal was clipped of hair and two sets of abrasions were made on the right side over the area of exposure sufficiently deep enough to penetrate the stratum corneum but not to disturb the derma. The left side was left intact. After the animals had been immobilized, 0.5 g of the suspension was applied under four patches placed on the backs of the animals (2 patches on the left side/2 patches on the right side). Following 24 hours of exposure, the patches were removed, any remaining material was wiped off, and the resulting reactions were scored on a scale from 0-4 using the Draize method (0=no erythema/no edema, 4=severe erythema/severe edema). In addition to this examination, the sites were scored on days two through seven.

The solution of BTCA, when applied to the intact and abraded skin of the rabbits, produced a barely perceptible to slight skin response. At 24 hours, 5 animals showed a barely perceptible erythema (score=1) with no edema formation, and one animal showed moderate erythema (score=2) with a slight edema (score=1). Steady reduction of the response was noted throughout the 7-day observation period, and with the exception of slight erythema along the abrasions in one animal, all reactions disappeared completely by day seven. Also, none of the usual sequelae to irritation, such as desquamation and drying, were observed during the course of the study. No essential differences were seen between reactions on intact and abraded skin areas. According to the Federal Hazardous Substances Act, a primary irritant is a substance that produces a skin reaction of five or greater. Based on an irritation index of 0.9 (the primary irritation index for this substance was determined using average Draize scores), BTCA was not classified as a primary skin irritant. No information was reported for control groups [Scientific Associates, Inc., 1980d].

ocular, rabbits
Nine New Zealand White rabbits of either sex were used to determine the type and extent of ocular reaction resulting from the administration of BTCA to the conjunctival sac. One-tenth of a milligram of undiluted powdered test chemical was placed in one eye of each animal, and the eye was held shut for one second. The other eye was left untreated as a control. Twenty seconds after application, the treated eyes of three animals were rinsed for one minute with warm tap water. The treated eyes of the remaining six animals were left unwashed for 24 hours, at which time they were examined, and rinsed with isotonic saline. The eyes were examined and the grade of ocular reaction recorded at 1, 24, 48, 72, and 96 hours, and at 7, 10, and 14 days. In addition, the treated eyes of all nine rabbits were further examined at each time point by placing one drop of 2% fluorescein sodium on the cornea to detect corneal lesions. After 15 seconds, this solution was washed out with isotonic saline. Application of BTCA to the eyes of three rabbits followed by a tap water rinse after 20 seconds, produced an ocular reaction within 24 hours. The reaction consisted of a slight to moderate erythema of the bulbar and palpebral conjunctivae, a moderate to severe chemosis of the lids, a slight to moderate accumulation of watery-mucoid discharge, and a slight to moderate corneal opacity involving 1/4 to 1/2 of the corneal surface. At 48 hours, the reaction of the conjunctivae became more intense for each animal, while the corneal reaction in one animal disappeared, was

decreased in another, and became more intense in the third. By 96 hours, only slight improvement was noted. At 7 days, two animals showed only slight erythema and the third continued to have corneal opacity. At the 14-day observation point, two animals were reaction-free, and the third exhibited erythema, chemosis, and corneal opacity. Vascularization was noted in two animals at 96 hours that continued through day 14. The maximum average score of 26.7 was recorded at 48 hours.

Application of BTCA to the eyes of six rabbits without an accompanying rinse produced severe ocular damage after 24 hours. The reactions included slight to moderate erythema of the bulbar and palpebral conjunctivae, severe chemosis of the lids, a moderate to marked accumulation of watery-mucoid discharge, and moderate to marked corneal opacity involving 1/4 or all of the corneal surface. The reactions were more severe at 48 and 72 hours, with 5/6 animals developing iritis. The maximum reaction was noted at 72 hours (average score of 85.3), but only slight improvement was noted throughout the 14-day test period. Vascularization of the cornea was observed initially at 96 hours that continued to increase through day 14.

Under both conditions described, BTCA was found to be an eye irritant, causing permanent ocular damage [Scientific Associates, Inc., 1980e].

C. Prechronic

1. Human Data

No data were found.

2. Animal Data

No data were found.

D. Chronic/Carcinogenicity

1. Human Data

No data were found.

2. Animal Data

No data were found.

E. Reproductive Effects and Teratogenicity

1. Human Data

No data were found.

2. Animal Data

No data were found.

F. Genetic Toxicology

1. Prokaryotic Data

No data were found.

2. Eukaryotic Data

No data were found.

G. Other Toxicological Effects

1. Immunotoxicity

No data were found.

2. Neurotoxicity

No data were found.

3. Biochemical Toxicology

rat liver mito-chondria
A large number of compounds, including 1,2,3,4-butanetetracarboxylate, were tested for their effectiveness as inhibitors of the tricarboxylate and dicarboxylate transporting systems of rat liver mitochondria, as monitored by citrate/[^{14}C] citrate exchange and phosphate/[^{14}C] L-malate exchange, respectively. For examination of citrate/[^{14}C] citrate exchange, mitochondria loaded with [^{14}C] citrate were incubated in a medium containing 10mM (final concentration) 1,2,3,4-butanetetracarboxylate in the presence of 2 mM citrate for two minutes at 0°C. In the case of mitochondria loaded with [^{14}C] L-malate, incubations were performed at 10°C for two minutes using 5 mM inorganic phosphate as the exchanger and 10mM (final concentration) 1,2,3,4-butanetetracarboxylate as the inhibitor. For control experiments, the exchanging ion (2mM citrate or 5mM phosphate) was added in the absence of 1,2,3,4-butanetetracarboxylate. Results were recorded as percentage exchange in the given time period.

As measured by the citrate/[^{14}C] citrate exchange, 1,2,3,4-butanetetracarboxylate was found to be a poor inhibitor of the tricarboxylate transporting system of rat liver mitochondria, inhibiting only 14% of the exchange system. This compound was also a poor inhibitor of the dicarboxylate transporting enzyme systems, inhibiting only 12% of the phosphate/[^{14}C] L-malate exchange. The authors report that the numerical values reported for the percentage exchange provide only a semi-quantitative indication of inhibitor potency. Because initial rate determinations were not made, the relative potencies of the inhibitors tested cannot be reported as Ki values. [Robinson *et al.*, 1972].

VI. STRUCTURE ACTIVITY RELATIONSHIPS

No data were found.

VII. REFERENCES

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APPENDIX I. ON-LINE DATABASES SEARCHED

	DATE OF SEARCH	TIME PERIOD
BRS:		
HZDB	January, 1991	current
CIS:		
TSCAPP	January, 1991	
DIALOG:		
ABI Information	January, 1991	1971-1991
Aerospace	January, 1991	1962-1991
Biosis Previews	January, 1991	1969-1991
Biotech Abstracts	January, 1991	1982-1990
CAB Abstracts	January, 1991	1972-1991
Chem Bus Newsbase	January, 1991	1984-1991
Chicago Tribune	January, 1991	1988-1991
CIN	January, 1991	
Compendex Plus	January, 1991	1970-1991
CRIS USDA	January, 1991	
Current Contents	January, 1991	
Dissertation Abstracts	January, 1991	1961-1991
Embase	January, 1991	1974-1991
Energy Sci & Technology	January, 1991	1983-1991
F & S Index	January, 1991	1980-1991
Federal Res in Progress	January, 1991	
Fine Chemicals	January, 1991	
Medline	January, 1991	1966-1991
NSA	January, 1991	1948-1991
NTIS	January, 1991	1964-1991
Paperchem	January, 1991	1967-1990
Pascal	January, 1991	1983-1990
Piers Imports	January, 1991	1989-1991
PTS Newsletter	January, 1991	1987-1991
PTS Prompt	January, 1991	1972-1991
Scisearch	January, 1991	1974-1991
Textile Technology Digest	January, 1991	1978-1991
Trade and Industry ASAP	January, 1991	1983-1991
Toxline	January, 1991	1965-1991
World Textiles	January, 1991	1970-1990
World Translations Index	January, 1991	1984-1990

MEAD:		
Nexis/Lexis-BNA ENV	February, 1991	
NLM:		
Chemid	January, 1991	
Chemline	January, 1991	
HSDB	January, 1991	
RTECS	January, 1991	
IRIS	January, 1991	
Toxline	January, 1991	1981-1980
Toxline 65	January, 1991	pre 1965-1980
Toxlit	January, 1991	1981-1991
Toxlit 65	January, 1991	1965-1980
Dart	January, 1991	1989-1991
Eticback	January, 1991	1950-1989
Emicback	January, 1991	1950-1991
CCRIS	January, 1991	
STN:		
Beilstein	January, 1991	1930-1979
CA	January, 1991	1967-1991
CAold	January, 1991	pre 1965
CA Previews	January, 1991	Updated weekly
Chemlist	January, 1991	1979-1991
CSCHEM	January, 1991	
Registry	January, 1991	

APPENDIX II. SAFETY INFORMATION

HANDLING AND STORAGE

1,2,3,4-Butanetetracarboxylic acid is stable under normal laboratory conditions, unstable in the presence of excessive light and heat [American Tokyo Kasei, Inc., 1986], and is classified as an irritant [Aldrich, 1990; Lenga, 1988]. This compound is incompatible with strong oxidizing agents [Lenga, 1988]. BTCA is to be stored in a cool, dry, dark area [American Tokyo Kasei, Inc., 1986]. BTCA has low volatility [Welch and Andrews, 1988].

EMERGENCY FIRST AID PROCEDURES

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently was affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.

PROTECTIVE EQUIPMENT

Eye: Safety goggles

Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or the NTP Health and Safety Minimum Requirements.

Respiratory Protection: A NIOSH-approved chemical cartridge respirator with an organic vapor and high-efficiency particulate filter cartridge.

EXTINGUISHANT

Dry chemical, carbon dioxide or halon extinguisher.

MONITORING PROCEDURES

There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for BTCA.

SPILLS AND LEAKAGE

Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

If BTCA is spilled the following steps shall be taken:

1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.
2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.
3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.
4. Dispose of all absorbed material as hazardous waste.

DECONTAMINATION OF LABORATORY EQUIPMENT

TDMS Terminal:	Whenever feasible, a protective covering (e.g.,plastic wrap) shall be placed over the keyboard when in use.
General Equipment:	Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

WASTE MANAGEMENT AND DISPOSAL PROCEDURES

Waste Management:	If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemical's in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.
Waste Disposal:	Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.