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Sulfate

SUMMARY

Inorganic sulfate (SO_4^{2-}) is required for the synthesis of 3'-phosphoadenosine-5'-phosphosulfate (PAPS). PAPS is required for synthesis of many important sulfur-containing compounds, such as chondroitin sulfate and cerebroside sulfate. While significant levels of sulfate are found in foods and various sources of drinking water, the major source of inorganic sulfate for humans is from biodegradation due to body protein turnover of the sulfur amino acids methionine and cysteine. Dietary sulfate in food and water, together with sulfate derived from methionine and cysteine found in dietary protein and the cysteine component of glutathione, provides sulfate for use in PAPS biosynthesis. Sulfate requirements are thus met when intakes include recommended levels of sulfur amino acids. For this reason, neither an Estimated Average Requirement (and thus a Recommended Dietary Allowance) nor an Adequate Intake for sulfate is established.

Adverse effects have been noted in individuals whose drinking water source contains high levels of inorganic sulfate. Osmotic diarrhea resulting from unabsorbed sulfate has been described and may be of particular concern in infants consuming fluids derived from water sources with high levels of sulfate. Some association between increased hydrogen sulfide production and risk of ulcerative colitis has been noted as well, but has not been adequately evaluated. Overall, there is insufficient information available to set a Tolerable Upper Intake Level for sulfate.

BACKGROUND INFORMATION

Sulfur is the 14th most abundant element in the earth's crust. Sulfate is produced in the environment from the oxidation of elemental sulfur, sulfide minerals, or organic sulfur. Soils are thought to average 850 mg of sulfate/kg and sea water 885 mg of sulfate/L (Field, 1972). Industrial sulfate results from the burning of sulfur-containing fossil fuels, household wastes (e.g., detergents), and effluents from tanneries, steel mills, sulfate-pulp mills, and textile plants. Sulfuric acid accounts for an estimated 80 percent of commercial sulfur production (NRC, 1980). Additionally, thousands of tons of sulfate compounds are produced each year; annual production of sodium sulfate was estimated at 792 tons in 1987 (EPA, 1990).

Most public water supplies contain sulfate concentrations of less than 500 mg/L (EPA, 2001). Sulfate levels in water around 250 mg/L and above are detectable due to an off odor and taste, and this generally causes those exposed to water with higher concentrations of sulfate to switch to bottled water sources for drinking. Still, adaptation to water with a high sulfate content is known to occur. Extremely high sulfate concentrations in water have been recorded; for example, 1,500 mg/L in a coal mine in Pennsylvania and 63,000 mg/L in a zinc mine in Idaho (Moore, 1991).

Sulfur dioxide (SO₂) emissions represent a growing concern for industrialized countries. Sulfur dioxide in the air can react with atmospheric water to produce sulfuric acid, resulting in acid rain (Drever, 1988). This can lead to increased soil acidity and elevated levels of sulfate in ground water (Drever, 1988). Moore (1991) estimated that global SO₂ emissions have more than doubled over the last 50 years.

Sulfate improves growth in farm animals consuming diets deficient in sulfur amino acids and very low in sulfate. Thus sulfate salts are sometimes used as growth-promoting feed additives for chickens, turkeys, and pigs.

Function

Sulfate is produced in the body from the transsulfuration of methionine to cysteine, followed by the oxidation of cysteine to pyruvate and inorganic sulfate. These processes occur as a result of protein turnover, as well as from degradation of excess protein-derived methionine or cysteine. Inorganic sulfate also results from the metabolism of several organic and inorganic sulfur compounds present

in food and water. Glutathione, an important antioxidant compound, is one of the more studied nonprotein organic sources of sulfate in the diet.

There are hundreds of sulfur-containing compounds in the human body, and the body synthesizes all of them, with the exception of the vitamins thiamin and biotin. Precursors include sulfate obtained from dietary intake and ingestion of the indispensable amino acids methionine and cysteine (cysteine is considered conditionally indispensable) (Shils et al., 1999).

One of the important roles for sulfate is in the biosynthesis of 3'-phosphoadenosine-5'-phosphosulfate (PAPS). Inorganic sulfate is required along with adenosine triphosphate. PAPS, also known as active sulfate, is used in the biosynthesis of many essential body compounds (Box 7-1), some of which are not absorbed intact when present in foods.

Physiology of Absorption and Metabolism

Gastrointestinal absorption of sulfate can occur in the stomach, small intestine, and colon (Anast et al., 1965; Batt, 1969; Cardin and Mason, 1975, 1976; Cole and Evrovski, 2000; Kandylis, 1983; Kaneko-Mohammed and Hogben, 1964). Absorption is a sodium-dependent active process (Ahearn and Murer, 1984; Florin et al., 1991; Langridge-Smith et al., 1983). When soluble sulfate salts (e.g., potassium sulfate or sodium sulfate) are consumed, more than 80 percent of oral sulfate doses are absorbed, as shown by isotopic tracer studies (Bauer, 1976; Florin et al., 1991).

With insoluble sulfate salts, such as barium sulfate, almost no absorption occurs (Ahmed and Hamza, 1989). When magnesium sul-

BOX 7-1 Examples of Compounds Biosynthesized Using 3'-Phosphoadenosine-5'-Phosphosulfate

- Chondroitin sulfate
- Dermatan sulfate
- Keratan sulfate
- Heparan sulfate
- Cerebroside sulfate
- Tyrosine-o-sulfate
- Tauroolithocholate sulfate (bile salt)
- Estrone 3-sulfate

fate is used to promote osmotic diarrhea, sulfate absorption is inversely proportional to the extent of the osmotic effect. Sulfate that is not absorbed in the upper gastrointestinal tract passes to the large intestine and colon, where it is either excreted in the feces, reabsorbed, or reduced by anaerobic bacteria to metabolites, such as hydrogen sulfide (Pitcher and Cummings, 1996; Roediger et al., 1997).

Because the majority of body sulfate is obtained from the ingestion of protein-derived methionine and cysteine and because the primary route of sulfate excretion is in the urine, 24-hour urinary sulfate excretion is strongly correlated with 24-hour urinary excretion of urea, the end product of dietary protein metabolism (Greer et al., 1986; Houterman et al., 1997; Sabry et al., 1965). Urinary sulfate excretion has recently been suggested as a measure of sulfur amino acid metabolism in humans (Hamadeh and Hoffer, 2001; Hoffer, 2002).

If one assumes that adults whose dietary protein needs are being met will consume a daily intake of 2 g of methionine and 2 g of cysteine, an equal amount of methionine and cysteine would be oxidized, producing 960 mg of sulfur, or 2.8 g/day of inorganic sulfate. A daily intake of inorganic sulfate as high as 1.3 g/day can be obtained from water and other beverages ($0.5 \text{ g/L} \times 2.6 \text{ L/day}$). A quantity of sulfate greater than this amount would likely be produced daily from metabolism of methionine and cysteine in food plus that derived from body protein turnover. An analysis of the sulfate content of various diets using foods purchased at supermarkets suggests a large variation in daily inorganic sulfate intake, ranging from 0.2 to 1.5 g (2.1–15.8 mmol)/day¹ (Florin et al., 1991). Metabolism of organic sulfur compounds, such as methionine and cysteine, supplies over half of the sulfate; the remainder is supplied from preformed sulfate in water and foods (see Table 7-1).

Clinical Effects of Inadequate Intake

Extensive work with laboratory animals has shown that growth is stunted when dietary sulfate is purposely eliminated from both the food and water supply and when sulfur amino acids, particularly cysteine, are provided at levels resulting in deficiency signs. Importantly, the addition of sulfate to these deficient diets resulted in

¹ To convert mmol of sulfate to mg of sulfate, multiply mmol by 96.1 (the molecular weight of sulfate).

TABLE 7-1 Estimated Total Daily Intake of Sulfate

Source	Concentration in Source per g (mmol) of Sulfur Amino Acid	Daily Intake of Source	Daily Amount, g/d (mmol/d)
Dietary organic sulfur containing compounds (includes methionine and cysteine)	0.7 (7.3)	Average protein intake reported in NHANES III ^a is \approx 100 g/d, which provides \approx 4 g of sulfur amino acids	2.8 (29)
Sulfate in drinking water and beverages	0.1–0.5 g/L (1.0–5.2 mmol/L) of fluid	2.6 L ^b	0.26–1.3 (2.7–13) Average = 0.78 (7.8)
Inorganic sulfate in food	Varies	2–3 kg	0.2–1.5 (2.1–15.8) Average = 0.85 (8.8)
Estimated total sulfate			3.25–5.55 (33.8–57.8) Average = 4.40 (45.8)

^a Third National Health and Nutrition Examination Survey.

^b Estimated intake of drinking water and beverages for men and women from Chapter 4.

significant growth responses (Anderson et al., 1975; Byington et al., 1972; Gordon and Sizer, 1955; Machlin and Pearson, 1956; Sasse and Baker, 1974a, 1974b; Smith, 1973; Soares, 1974). In young animals, a minimal level of 165 to 200 mg of sulfate/kg of diet has been found to yield a maximal growth response in rats (Smith, 1973) or chicks (Sasse and Baker, 1974b) fed a diet limited in cysteine.

Using similar dietary conditions in adult men (low sulfate, sulfur amino acid-deficient diet), nitrogen retention increased when sodium sulfate was added to the diet in an amount equivalent to that provided by additional methionine (Zezulka and Calloway, 1976).

Under these conditions, sulfate is probably used directly for PAPS biosynthesis, thereby sparing cysteine such that more of the cysteine is made available for protein synthesis and growth. A recent study in which lower levels of serum sulfate were detected when acetaminophen was given with glucosamine sulfate to normal adults

provides additional support for a role of nonprotein sulfate in sulfation and metabolism of phenolic compounds (Hoffer et al., 2001). In humans, sulfate ingestion would almost always exceed 3 g/day as a result of sulfate ingestion in food and water, together with the sulfate produced in the body from metabolism.

INDICATORS CONSIDERED FOR ESTIMATING THE REQUIREMENT FOR SULFATE

Growth responses in chicks and rats occur when sulfate is added to low-sulfate diets that are deficient in cysteine (Byington et al., 1972; Sasse and Baker, 1974b); nitrogen retention is improved in humans placed under a similar dietary regimen (Zezulka and Calloway, 1976). Whether sulfate incorporation into 3'-phosphoadenosine-5'-phosphosulfate (PAPS), or whether PAPS synthase activity could be used as a measure of sulfate adequacy, is not known. The one human study conducted to date did not attempt to measure these parameters (Zezulka and Calloway, 1976). Because sulfate is an obligatory end product of sulfur amino acid turnover, inadequate sulfate consumption (or production) is unlikely to occur in any setting other than where protein deficiency is also present.

FACTORS AFFECTING SULFATE REQUIREMENTS

Limited information is available on the extent to which 3'-phosphoadenosine-5'-phosphosulfate (PAPS) biosynthesis can be affected by available inorganic sulfate. Whether increased amounts of PAPS are needed in diseases, such as arthritis, in which sulfated compounds (e.g., sulfates of glucosamine and chondroitin) are implicated is unknown because in most studies sufficient sulfur amino acids are provided as part of dietary protein (Hoffer et al., 2001). The primary factor affecting a dietary need for sulfate is the extent to which sulfur-containing compounds are available for degradation to provide sulfate for PAPS biosynthesis. Unlike most other nutrients, the body's need for sulfate can be met by consuming other required nutrients, sulfur amino acids. Thus a deficiency of sulfate is not found in humans consuming normal protein intakes with adequate sulfur amino acids. Ingestion of methionine, cysteine, and glutathione in foods, along with consumption of other sulfated compounds in both food and beverages, is sufficient to meet the body's requirement for sulfate.

Sulfate requirements for the growing fetus are high (Cole and

Evrovski, 2000; Cole et al., 1992), and this raises questions concerning sulfate requirements during pregnancy, particularly in situations where the mother is on a medication, such as acetaminophen, that is known to deplete sulfate (Morris and Levy, 1983).

FINDINGS BY LIFE STAGE AND GENDER GROUP

Sulfate intake (as well as sulfate produced via amino acid turnover) typically exceeds the need for 3'-phosphoadenosine-5'-phosphosulfate biosynthesis, as evidenced by maintenance of normal levels of urinary excretion of sulfate (Cole and Evrovski, 2000) when sulfur amino acids are adequate. Recommended intakes have already been established for sulfur amino acids, which would thus cover the need for inorganic sulfate (IOM, 2002/2005). Given these two points, neither an Estimated Average Requirement (and thus a Recommended Dietary Allowance) nor an Adequate Intake for sulfate is established.

INTAKE OF SULFATE

Sources

Approximately 19 percent of total sulfate comes from ingested inorganic sulfate from foods and 17 percent of total comes from inorganic sulfate in drinking water and beverages (Table 7-1). Many other sulfur compounds in food can yield inorganic sulfate as a result of degradation or turnover. Among organic compounds, methionine and cysteine in food proteins, glutathione in both animal and vegetable products (Wierzbicka et al., 1989), taurine in animal-source foods, lanthionine (a cross-linked sulfur amino acid produced when protein-bound cysteine undergoes heat treatment at an alkaline pH), and sulfated glycosaminoglycans in both plant- and animal-derived foods are important contributors of organic sulfate, providing the remaining approximately 64 percent of total sulfate available for body needs.

Other organic sulfur compounds are ingested in certain situations. Several drugs contain sulfur, and several cysteine derivatives are used in certain clinical situations. For example, N-acetyl-L-cysteine is used as a mucolytic agent for treating sepsis, respiratory diseases, and various autoimmune deficiency diseases (Baker and Wood, 1992; Kelly, 1998). Sulfur-containing D-penicillamine or dimercaptopropanol is used for treating the copper toxicity problems seen in Wilson's disease (Smithgall, 1985). Also, small quanti-

ties of S-methylmethionine are present in many foods (Kovatscheva and Popova, 1977). Some individuals self-medicate with sulfur-containing compounds, such as chondroitin sulfate, glucosamine sulfate, and methylsulfonylmethane, for a possible benefit to bones and joints. Evidence has been presented suggesting that the beneficial effects of glucosamine sulfate for osteoarthritis may be due more to the sulfate than to the glucosamine contained in this compound (Hoffer et al., 2001).

The sulfate content of a few foods and beverages has been estimated (Tables 7-2 and 7-3) by Florin et al. (1993). Their analytical procedures involved acid hydrolysis; thus their sulfate values were referred to as “available” sulfate and would include not only free anionic sulfate, but also that liberated from various ester sulfates, such as amino sulfonates (e.g., heparin), nitric oxide-sulfonates (e.g., glucosinolates), phospho-sulfonates (e.g., 3'-phosphoadenosine-5'-phosphosulfate), sulfuryl-sulfonates (e.g., cysteine sulfosulfate), and oxy-sulfonates (e.g., mucin and sulfate-conjugated bile acids, but not carbo-sulfonates (e.g., taurine). Thus the methodology was designed to mimic the digestive process in-

TABLE 7-2 Sulfate Content of Selected Foods

Food	Number of Samples	Mean Sulfate Content, mg/g (standard deviation)
Almonds	4	0.9 (0.61)
Bread, commercial brown wheat	14	1.5 (0.46)
Bread, commercial white	6	1.3 (0.31)
Broccoli	4	0.9 (0.69)
Brussels sprouts	3	0.9 (0.085)
Cabbage	4	0.8 (0.078)
Cauliflower	4	0.5 (0.41)
Dates	4	1.1 (0.54)
Dried apples	3	4.9 (0.4)
Dried apricots	2	3.0 (1.5)
Dried potato	4	2.0 (0.74)
Flour, soya	3	1.2 (0.25)
Pasta, durum wheat	3	0.3 (0.25)
Peanuts	4	0.7 (0.16)
Prunes	2	1.0 (1.2)
Raisins	4	1.3 (0.29)
Sausage, English style	3	1.0 (0.11)
Sunflower seeds	3	0.6 (0.075)

SOURCE: Florin et al. (1993).

TABLE 7-3 Sulfate Content of Selected Beverages

Beverage	Number of Samples	Sulfate Content, Mean (mg/L)
Beer, bitter	7	260 (64)
Beer, lager	4	130 (33)
Cider	3	270 (60)
Coconut milk	4	500 (160)
Cola	4	80 (66)
Juice, apple	6	70 (13)
Juice, grape (red, white)	4	200 (110)
Juice, tomato	3	250 (170)
Milk, cow	4	100 (18)
Milk, human ^a	38	5 (0.9)
Milk, infant formula ^a	16	66 (9)
Wine, red	8	380 (90)
Wine, white	6	300 (110)

^a From Hoppe et al. (1998).

SOURCE: Florin et al. (1993).

volving gastric acid and intestinal and bacterial enzymes that release sulfate from sulfate esters in food.

A wide range of "available" sulfate values were estimated from different foods, but particularly high levels (> 1 mg/g) were found in some fruits, soya flour, certain breads, and sausages. Among beverages, several juices, beers, wines, and ciders were found to contain more than 250 mg of sulfate per L. Among inorganic sulfur sources in the food and water supply, sulfate itself, along with sulfite (SO_3^{2-}), predominate, the latter being a food additive that functions as a preservative. Sulfite can also occur naturally as a consequence of fermentation (e.g., in wine). Sulfite is easily oxidized to sulfate, either in food itself or in the gut following consumption. Moreover, sulfite, as well as other inorganic sulfur compounds in the +4 valence state (e.g., SO_2 , HSO_3^{1-}) are highly bioactive and have well-known toxic side effects (Til and Feron, 1992; Wedzicha, 1992).

Sulfate ingestion from drinking water is highly variable and depends on the area of the country from which the water is obtained. Some well water in rural areas of the United States has been known to contain upwards of 500 mg/L (Moore, 1952), and some of the "mineral" waters sold with health claims have been reported to exceed this level (Allen et al., 1989). Distilled water contains very little, if any, sulfate, and deionized water contains no sulfate.

Human milk is very low in sulfate (5 mg/L), and even though an average value for infant formula products (both milk- and soy-based) was found to be 13 times higher than that in human milk (66 mg/L), these levels of sulfate are still lower than those in many sources of drinking water (Hoppe et al., 1998).

Intake

Surveys of sulfate intake from food and beverages are currently not available. The Third National Health and Nutrition Examination Survey has not estimated sulfate intake directly. Indirect estimates of sulfate intake can be calculated from the intakes of sulfur-containing amino acids. Table 7-4 provides estimates of sulfate intake that would be derived from metabolism of cysteine and methionine. The estimates provided in the table thus do not include sulfate from food, beverages, or drinking water, nor that derived from organic sulfur compounds other than methionine and cysteine.

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Diarrhea

Adult Human Data. Osmotic diarrhea and loose stools have been reported with high intakes of sulfate consumed in water (Backer, 2000). Such adverse effects are usually short term, but they may be more severe in infants. The U.S. Environmental Protection Agency (EPA) and the Centers for Disease Control and Prevention (CDC) collaborated in a 1997 study to determine whether high levels of sulfate in drinking water would cause diarrhea or other gastrointestinal disturbances in infants and in adults categorized as “transients” (i.e., those experiencing an abrupt change in water sulfate concentration from low to high) (EPA, 1999a). The study involved 105 adult volunteers from Atlanta, Georgia, including CDC and EPA employees, who were randomly assigned to one of five possible sulfate exposure groups. Sulfate concentrations (from sodium sulfate) tested in drinking water were 0, 250, 500, 800, and 1,200 mg/L. Participants were given water for 6 days. The water provided for days 1, 2, and 6 of the 6-day study contained no added sulfate, whereas the water provided for days 3, 4, and 5 contained added

TABLE 7-4 Mean and Percentiles of Sulfate (g) Derived from the Usual Daily Intake of Sulfur-Containing Amino Acids

Sex/Age Category ^a	n	Mean	Percentile	
			1st	5th
Both sexes, 2–6 mo	793	0.41	0.14	0.21
Both sexes, 7–12 mo	827	0.76	0.21	0.21
Both sexes, 1–3 yr	3,309	1.24	0.28	0.49
Both sexes, 4–8 yr	3,448	1.58	0.90	1.07
M, 9–13 yr	1,219	2.07	1.15	1.37
M, 14–18 yr	909	2.53	1.21	1.53
M, 19–30 yr	1,902	2.78	1.58	1.88
M, 31–50 yr	2,533	2.56	1.31	1.61
M, 51–70 yr	1,942	2.22	0.90	1.20
M, 71+ yr	1,255	1.85	0.81	1.04
F, 9–13 yr	1,216	1.66	1.25	1.36
F, 14–18 yr	949	1.59	0.58	0.83
F, 19–30 yr	1,901	1.71	0.92	1.11
F, 31–50 yr	2,939	1.72	0.98	1.16
F, 51–70 yr	2,065	1.55	0.72	0.92
F, 71+ yr	1,368	1.40	0.64	0.83
Pregnant	346	2.07	1.22	1.44
Lactating	99	2.45	1.71	1.92
P/L	440	2.16	1.30	1.51
All individuals	28,575	1.94	0.74	0.99
All individuals (+P/L)	29,015	1.95	0.76	1.01

^a M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Sulfate content calculated using 0.7 g sulfate/g of sulfur amino acid from the Third National Health and Nutrition Examination Survey (1988–1994) intake data for cysteine and methionine.

DATA SOURCE: IOM (2002/2005).

sulfate. While the study did not indicate how much water was consumed, nor the season of the study, there were no statistically significant differences in the number of bowel movements for days 1, 2, and 6 compared with those for days 3, 4, and 5. In regression analyses of diarrhea frequency by sulfate dose (dose/kg of body weight), sulfate intake was not a significant predictor of diarrhea.

Evaluation of data from 248 private wells in North Dakota indicated that 62 percent of consumers experienced a laxative effect when the sulfate concentration in the well water exceeded 1,000 mg/L (Moore, 1952). Two studies in healthy adults were reported by Heizer and colleagues (1997). Four participants in the dose-

10th	25th	50th	75th	90th	95th	99th
0.21	0.28	0.35	0.49	0.70	0.77	1.33
0.35	0.49	0.70	0.98	1.33	1.54	2.03
0.63	0.91	1.19	1.54	1.96	2.17	2.80
1.16	1.34	1.55	1.79	2.02	2.17	2.48
1.51	1.74	2.02	2.37	2.70	2.91	3.36
1.71	2.04	2.46	2.95	3.43	3.73	4.37
2.05	2.36	2.74	3.15	3.58	3.84	4.41
1.79	2.11	2.49	2.93	3.40	3.70	4.33
1.39	1.72	2.13	2.62	3.16	3.56	4.45
1.20	1.45	1.78	2.16	2.58	2.88	3.54
1.42	1.53	1.65	1.79	1.90	1.98	2.14
0.97	1.22	1.53	1.90	2.29	2.55	3.11
1.22	1.41	1.68	1.97	2.25	2.43	2.82
1.27	1.46	1.69	1.94	2.20	2.37	2.71
1.04	1.25	1.51	1.81	2.11	2.31	2.74
0.94	1.13	1.37	1.63	1.90	2.09	2.47
1.55	1.77	2.04	2.32	2.62	2.81	3.18
2.03	2.23	2.44	2.67	2.88	3.01	3.26
1.65	1.86	2.13	2.43	2.70	2.88	3.23
1.15	1.45	1.85	2.33	2.84	3.18	3.91
1.16	1.46	1.86	2.33	2.84	3.18	3.90

ranging study were given six sulfate doses (in water) of 0, 400, 600, 800, 1,000, or 1,200 mg/L for six consecutive 2-day periods, while six other subjects in a single-dose study received sulfate doses (in water) of 0 and 1,200 mg/L for two consecutive 6-day periods. In the dose-ranging study, the mean sulfate intake coming from drinking water in the 1,200 mg/L group was 2.7 g, while the mean sulfate intake in drinking water in the single-dose study at 1,200 mg/L was 2.9 g due to differences in total water consumed. In both studies at the 1,200-mg/L sulfate dose, a small increase in stool mass occurred, but no complaints of diarrhea or changes in stool frequency were reported.

Severe diarrhea in five healthy men was reported when they were given 8 g of sodium sulfate (6.7 g of sulfate) as a single dose; however, little or no diarrhea occurred when divided into four equal hourly doses (Cocchetto and Levy, 1981).

Magnesium salts have been prescribed as a cathartic. Although magnesium hydroxide and magnesium oxide are the primary salts utilized for this purpose, magnesium sulfate (Epsom salts) is also used. These poorly absorbed ions exert an osmotic effect in the intestinal lumen and cause water to be retained, thus increasing the fluidity of the intraluminal contents (Izzo et al., 1996). High oral doses of magnesium sulfate can lead to severe magnesium toxicity in patients with impaired renal function, but toxicity is uncommon in healthy individuals (Mordes, 1978). The bioavailability of magnesium was examined following a large oral dose of 13.9 g (56.5 mmol) of magnesium sulfate over a 4-hour period in six men (Morris et al., 1987). All subjects experienced mild to moderate diarrhea. While the magnesium was poorly absorbed (only 6.9 percent of the oral dose was absorbed by 72 hours), approximately 38 percent of sulfate appeared in the urine. The comparatively poor absorption of magnesium thus may be the primary ion responsible for the diarrhea seen since absorption of sulfate was much greater.

TABLE 7-5 Case Reports of Infants Exposed to High Levels of Sulfate

Subject	Sulfate in Water Supply (mg/L)	Median Weight ^a (kg)	Water Intake ^b (mL/d)	Sulfate Dose (mg/kg)	Sulfate Dose (mg/d)
5-mo-old boy	630	7.3	848	73	534
10-mo-old boy	720	9.7	896 ^c	66	645
1-yr-old girl	1,150	9.5	906	110	1,042

^a Median weights from Kuczmarowski et al. (2000).

^b Fiftieth percentile of daily intake of drinking and beverage water (Appendix Table D-3).

Infant Human Data. A number of studies have been conducted in human infants and very young animals because of their vulnerability to the adverse consequences of osmotic diarrhea. One study of 274 infants aged 6.5 to 30 weeks in 19 South Dakota counties involved data on frequency of diarrhea (Esteban et al., 1997). One hundred seventy households participating in the study also submitted water samples. The median sulfate level of the water samples was 264 mg/L. In approximately 83 percent of the households that submitted water samples, no significant association was found between sulfate ingestion and the reported incidence of diarrhea. The median sulfate concentration of water samples and the mean daily sulfate intake for infants who did not develop diarrhea were 258 mg/L and 29 mg/kg/day, respectively. For infants who developed diarrhea, the median water sulfate concentration was 289 mg/L, and the mean daily sulfate intake was 28 mg/kg/day. At least one small case-history study suggested that infants exposed to water sulfate concentrations above 600 mg/L may develop diarrhea (see Table 7-5) (Chien et al., 1968).

Pregnant Animal Data. Only one study of the effect of sulfate on animals during pregnancy was found. In a swine study, water con-

Comments

Developed frequent green and watery stools promptly after consuming formula made with well water; prior to consumption, the infant tended to be constipated

Developed watery brown stools promptly after consuming formula made with well water; stools contained no bacterial pathogens, ova, or parasites

Developed persistent diarrhea after several days of consuming well water; parents and two siblings developed intermittent diarrhea after consuming well water for 1 wk; stools contained no bacterial pathogens, ova, or parasites

^c Mean of daily intake of drinking and beverage water for infants and children 7-12 mo and 1-3 yr of age (Appendix Table D-3).

SOURCE: Chien et al. (1968).

taining 320, 1,800, or 3,300 mg/L of sulfate (as sodium sulfate) was provided to sows during the last 84 days of gestation and throughout a 28-day lactation period (Paterson et al., 1979). No effects on stool consistency were apparent in either sows or first-litter gilts.

Pregnant Human Data. Magnesium sulfate is administered parenterally in various clinical situations, particularly as a preventative measure for eclampsia during pregnancy. Although deemed to be safe and effective, Ricci and coworkers (1990) observed that serum sulfate concentration increased approximately twofold in 11 pregnant women treated with magnesium sulfate.

Young Animal Data. A sulfate dose-response study in neonatal artificially reared piglets added doses of sulfate (from sodium sulfate) to the liquid diet ranging from 0 to 2,200 mg/L (0 to \approx 2,640 mg/kg of body weight)/day (Gomez et al., 1995). The basal diet contained 270 mg/L (\approx 325 mg/kg)/day of sulfate from dietary ingredients (deionized water was used to prepare the liquid diets). While neither growth rate nor voluntary dietary intake during the 18-day study was affected by sulfate dose, nonpathogenic diarrhea became evident at sulfate concentrations greater than 1,200 mg/L (based on an estimated water intake of \approx 1,440 mg/kg/day). Diarrhea occurred in 50 percent of the piglets receiving 1,600 to 1,800 mg/L (\approx 1,920 to 2,160 mg/kg)/day, and in all piglets receiving 2,000 to 2,200 mg/L (\approx 2,400 to 2,640 mg/kg)/day of supplemental sulfate. Urinary sulfate reached a maximum concentration at 1,600 mg/L (\approx 1,920 mg/kg)/day of oral sulfate supplementation. From these data it was inferred that sulfate at an intake above 1,600 mg/L (\approx 1,920 mg/kg)/day was osmotically active due to malabsorption.

Sulfate-supplemented water was also provided to piglets for a longer time period, from 28 days of age (weaning) to 56 days of age; the sulfate concentration was 3,000 mg/L (based on estimated water intake, \approx 354 to 378 mg/kg body weight/day) provided as sodium sulfate or as a 1:1 mixture of sodium sulfate and magnesium sulfate (Paterson et al., 1979). Fecal scoring indicated that both sulfate regimens resulted in a higher incidence of loose stools and intermittent diarrhea compared with the control piglets.

Acidosis

Metabolic acidosis has been shown to result from consumption of "flowers of sulfur," a fine, yellow powder that is more than 99.5 percent pure sulfur (Blum and Coe, 1977; Schwartz et al., 1986).

Magnesium sulfate is given intravenously in various clinical situations, particularly to prevent eclampsia during pregnancy. Although deemed to be safe and effective when used in this therapeutic mode, serum sulfate concentration was increased approximately twofold in 11 pregnant women treated with magnesium sulfate (Ricci et al., 1990). No reports of acidosis as the result of consuming the dietary supplement chondroitin sulfate were found.

Ulcerative Colitis

Sulfate and undigested sulfur compounds have been implicated in the etiology of ulcerative colitis (Magee et al., 2000; Pitcher and Cummings, 1996; Roediger et al., 1997). The specific agent is thought to be hydrogen sulfide, which is produced in the colon from sulfate by sulfate-reducing bacteria. Sulfate-reducing bacteria use either sulfate or sulfite as a terminal electron acceptor, releasing sulfide into the lumen where it is converted to hydrogen sulfide gas (H_2S) (Pitcher and Cummings, 1996). It is now clear that sulfate can also enter the colon from unabsorbed dietary sulfate as well as from unabsorbed sulfur amino acids, taurine, and sulfur-containing food additives (e.g., sulfur dioxide, sulfites, and carrageenan). A portion of the sulfate produced from amino-acid turnover can also reenter the gut from the circulation (Garcia and Stipanuk, 1992). Excess luminal sulfide is thought to overburden mucosal detoxification systems, resulting in impaired butyrate oxidation and colonic epithelial inflammation.

Sodium sulfate supplementation has been demonstrated to inhibit methaneogenesis and stimulate the growth of sulfate-reducing bacteria in the colon of humans (Christl et al., 1992). Experimentally, colitis has been produced in Guinea pigs and rabbits that were given degraded carrageenan, sodium lignosulfate, or sulfated amylopectin in their drinking water (Marcus and Watt, 1969, 1974). It was also produced in rats, mice, and hamsters by administration of dextran sulfate sodium (Carrier et al., 2002; Ohkusa, 1985; Okayasu et al., 1990).

Among the amino acids in protein, cysteine and cystine are well known to be among the poorest absorbed from the upper small intestine (NRC, 1994). Heat treatment of proteins contributes to the poor digestibility of cysteine because heating protein causes cysteine to be oxidized to cystine, a dimer that is poorly absorbed (Miller et al., 2001; Parsons et al., 1992).

These observations, together with the fact that fecal sulfide levels are elevated in ulcerative colitis patients (Florin et al., 1990; Pitcher

et al., 1995), add credence to the link between colonic sulfide levels and ulcerative colitis. Indeed, drug therapy involving 5-aminosalicylic acid (Pitcher et al., 1995; Roediger and Duncan, 1996) and gentamycin (Pitcher et al., 1994) for ulcerative colitis is known to suppress hydrogen sulfide production. Moreover, standard therapy for ulcerative colitis patients has included restriction of foods, such as milk, eggs, and cheese, that are significant sources of dietary sulfur (Truelove, 1961). More recently, dextran sulfate sodium-induced ulcerative colitis in rats was shown to be exacerbated by dietary iron supplementation, a potent oxidant, but was ameliorated by vitamin E supplementation (Carrier et al., 2002). However, vitamin E supplementation did not affect oxidative stress, as measured by plasma and colonic lipid peroxides and glutathione peroxidase activity, thus suggesting another mechanism for reducing inflammation.

Dose-Response Assessment

Adults

Adverse effects that have been associated with sulfate ingestion include osmotic diarrhea and ulcerative colitis. Generally, a self-regulating effect occurs in that higher concentrations of water sulfate have an odor and off taste, which causes those exposed to water with a high sulfate content to use bottled water. Mineral water sources, however, can vary widely in both cation and anion concentration. Nonetheless, studies have shown that both demineralized bottled water and spring bottled water contain sulfate levels below 500 mg/L, with most lower than 250 mg/L (Allen et al., 1989; Ikem et al., 2002).

Short-term exposure (3 days) to sulfate levels in water (concentration 1,200 mg/L, which would lead to ingestion of 3.6 g of sulfate based on the median intake of water for 19- to 30-year-old men of 3 L/day [Appendix D]), did not induce noticeable diarrhea in the CDC/EPA study in healthy adults (EPA, 1999a). Regression analysis of diarrhea frequency by sulfate dose (dose/kg of body weight) found that sulfate dose was not a significant predictor of diarrhea (EPA, 1999a). Longer-term studies of 6 days in six healthy men showed little change at 2.9 g (1,200 mg/L)/day as well (Heizer et al., 1997). Severe diarrhea has been noted when 6.7 g of sulfate was given in a single dose, but was absent when provided in four divided doses (Cocchetto and Levy, 1981).

As described in the previous section, evidence on the role of sulfate in the etiology of ulcerative colitis is inconclusive. Also, available data make it difficult to rule out other factors that might be causative of colitis exacerbations. Hence it is not possible to identify a Tolerable Upper Intake Level (UL) for sulfate based either on diarrhea or on a possible role in ulcerative colitis.

Infants

In one study of infants, the reported occurrence of osmotic diarrhea did not vary by estimated intake of sulfate (Esteban et al., 1997). Those who developed diarrhea drank water with a median sulfate concentration of 289 mg/L, while those who did not have diarrhea drank water with a median sulfate concentration of 258 mg/L. Mean daily sulfate intake for infants who did not develop diarrhea was 29 mg/kg/day, while the mean daily sulfate intake of infants developing diarrhea was 28 mg/kg/day. In a small-case series, infants exposed to water sulfate concentrations above 600 mg/L (estimated intake about 66 mg/kg) did develop diarrhea (Chien et al., 1968).

Animal dose-response data using neonatal piglets may be relevant to infants. The study of Gomez and coworkers (1995) included doses of sulfate (from sodium sulfate) ranging from 0 to 2,200 mg/L (0 to 2,640 mg/kg of body weight/day) added to a liquid diet of 270 mg/L (≈ 325 mg/kg/day of sulfate in the basal diet). Nonpathogenic diarrhea became evident at sulfate concentrations greater than 1,200 mg/L ($\approx 1,440$ mg/kg)/day. Diarrhea occurred in 50 percent of the piglets receiving 1,600 to 1,800 mg/L ($\approx 1,920$ to 2,160 mg/kg)/day, and in all piglets receiving 2,000 to 2,200 mg/L ($\approx 2,400$ to 2,640 mg/kg)/day of supplemental sulfate.

Based on this study, a sulfate intake of up to 1,470 mg/L (amount/kg added + background = 1,200 + 270) did not lead to diarrhea. This level is equivalent to approximately 1,530 mg (1,470 \times 1.04 L)/day of sulfate (the piglets consumed a liquid diet containing 20 percent dry matter; 3.76 kg of dry matter was consumed over an 18-day feeding period, therefore piglets consumed on average 1.04 kg/day [(3.76 \div 0.2) \div 18 days] assuming that the density of the formula given was approximately 1 kg/L).

Overall, data are inadequate to set a UL for sulfate for infants. Based on neonatal piglet data, however, it would appear that levels exceeding 1,500 mg/day may cause some degree of diarrhea.

Special Considerations

Renal Failure. Increased serum sulfate levels are a common feature of kidney failure. Levels of serum sulfate may be elevated 7 to 24 times the normal level in an individual with acute renal failure. In end-stage renal disease, hemodialysis and peritoneal dialysis treatment remove sulfate, but serum sulfate levels are often still elevated (Cole and Evrovski, 2000; Holmes et al., 1960; Kirschbaum, 1998). Increased serum sulfate concentration results in increased complexation with calcium, and this may in part be responsible for the parathyroid stimulation that occurs in chronic renal disease (Cole and Evrovski, 2000; Michalk et al., 1981). The hypersulfatemia of chronic renal failure may directly affect the trans-sulfuration pathway and contribute to the severity of homocysteinemia typically seen in this condition (Nakanishi et al., 2002).

Hyperthyroidism. Hyperthyroidism increases basal metabolic rate which, in turn, increases protein catabolism. Increased serum sulfate levels have been noted in hyperthyroidism, probably due to increased breakdown of protein and thus sulfur amino acids (Tallgren, 1980). The implications of the hypersulfatemia associated with hyperthyroidism are unclear.

Risk Characterization

Based largely on taste considerations, the U.S. Environmental Protection Agency (EPA) recommends an upper limit of 250 mg/L for sulfate in drinking water. EPA has also recommended, but not required, that the maximum sulfate contaminant concentration be set at 500 mg/L for the prevention of acute onset of diarrhea (EPA, 2002b). This is the same maximum contaminant level as the Canadian standard (Health Canada, 2002). The maximum contaminant level sulfate standard of the World Health Organization is 400 mg/L (WHO, 1984).

The American Water Works Association has officially objected to these standards. The association's position is that if any maximum contaminant level is to be set for sulfate, it should be set at a level not less than 1,000 mg/L, and this should apply only to infants (AWWA, 1995).

In 1994, EPA estimated that 2,000 of the 54,000 public water systems in the United States had sulfate concentrations higher than 500 mg/L, and most of these occurred in systems serving populations of less than 10,000 people (EPA, 1999b). None of the public

water systems serving populations of over 100,000 people had sulfate levels that exceeded 500 mg/L. Currently, EPA has made a preliminary determination not to regulate sulfate in drinking water (EPA, 2002a).

RESEARCH RECOMMENDATIONS

- The relationship of urinary sulfate as a marker of sulfate absorption in evaluating adverse effects due to high intakes of sulfate.
- Sulfate supplementation of low-cysteine food products (e.g., casein-based enteral formula) to determine if supplementation improves growth or nitrogen balance.
- Sulfate needs during pregnancy, particularly the sulfate requirements of the growing fetus.
- Evaluation of using 3'-phosphoadenosine-5'-phosphosulfate or other biomarkers to determine dietary sulfate sufficiency.
- Better data on the relationship of diarrhea to sulfate intake in infants.
- The effects of acute versus chronic sulfate ingestion on diarrhea, as well as whether and at what point adaptation occurs.
- Survey studies comparing high versus low sulfate water ingestion from public water supplies that appropriately control for other causes of intestinal disturbances.
- Studies to evaluate whether chronic exposure to high sulfur (both cystine and sulfate) ingestion predisposes individuals to ulcerative colitis, and the role of hydrogen sulfide in its etiology.
- Studies to determine how much of the sulfate produced via turnover in metabolism reenters the bowel and thus may serve as an irritant or oxidant.
- Absorption studies using acute and chronic sulfate doses.
- Analytical studies to determine sulfate, as well as total sulfur content, of foods.

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