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Drinking Water Advisory: Consumer Acceptability Advice and Health Effects Analysis on Sulfate

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U.S. Environmental Protection Agency
Office of Water (4304T)
Health and Ecological Criteria Division
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FOREWORD

The Drinking Water Advisory Program, sponsored by the Health and Ecological Criteria Division of the Office of Science and Technology (OST), Office of Water (OW), provides information on the health and organoleptic (taste, odor, etc.) effects of contaminants in drinking water. The Drinking Water Advisory documents are a component of the OW Health Advisory Program. Drinking Water Advisories differ from Health Advisories because of their focus on aesthetic properties (e.g., taste, odor, color) of drinking water. A Drinking Water Advisory is prepared when contaminants cause adverse taste and odor influences at concentrations lower than those for adverse health effects.

A Drinking Water Advisory is not an enforceable standard for action. It describes nonregulatory concentrations of the contaminant in water that are expected to be without adverse effects on both health and aesthetics. Both Health Advisories and Drinking Water Advisories serve as technical guidance to assist Federal, State, and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. They are subject to change as new information becomes available. This draft supersedes any previous draft advisories for this chemical.

The Advisory discusses the limitations of the current database for estimating a risk level for sulfate in drinking water and characterizes the hazards associated with exposure. The Drinking Water Health Advisory value was developed by a panel of experts through a workshop held on September 28, 1998, and sponsored by the Centers for Disease Control (CDC) and the United States Environmental Protection Agency (U.S. EPA). The experts who participated in the workshop were:

Charles Abernathy, Ph.D. - U.S. EPA
David Cole, M.D., Ph.D. - University of Toronto
Marie Cassidy, Ph.D. - George Washington University
Marilyn Morris, Ph.D. - State University of New York: Buffalo
Guillermo Gomez, Ph.D. - North Carolina State University
Lorraine Backer, Ph.D. - National Center for Environmental Health at CDC

A workshop report was prepared that summarized the data considered at the workshop and its findings. This report was published by EPA as Document Number 815-R-99-002 in January 1999 (EPA, 1999b). The workshop report was externally peer reviewed by the following scientists (EPA, 1999c):

Laurence L. Brunton, Ph.D. - University of California San Diego
Paul E. Brubaker, Ph.D. - Brubaker Associates, New Jersey.
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ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
g	gram
kg	kilogram
L	liter
m^3	cubic meters
mg	milligram
min	minute
mM	millimolar
mmol	millimole
NTP	National Toxicology Program
OST	Office of Science and Technology
OW	Office of Water
PAPS	3′-phosphoadenosine-5′-phosphosulfate
ppm	parts per million
PWS	public water system
RfD	Reference Dose
SDWA	Safe Drinking Water Act
SDWIS/FED	Safe Drinking Water Information System/Federal
SO_4^{2-}	sulfate
SMCL	secondary maximum contaminant level
UCM	unregulated contaminant monitoring
µg	microgram
µmol	micromole

EXECUTIVE SUMMARY

The EPA Office of Water is issuing this advisory to provide guidance to communities that may be exposed to drinking water contaminated with high sulfate concentrations. The advisory provides an analysis of the current health hazard information and an evaluation of available data on the organoleptic (i.e., taste and odor) problems associated with sulfate-contaminated water, because organoleptic problems will affect consumer acceptance of water resources. This advisory does not recommend a Reference Dose (RfD) because of limitations of available data for assessing risks. However, the advisory does provide guidance on the concentrations above which health and organoleptic problems would likely occur. This Drinking Water Advisory does not mandate a standard for action; rather it provides practical guidelines for addressing sulfate contamination problems and supersedes previous draft advisories for sulfate

Conclusion and Recommendation

In order to enhance consumer acceptance of water resources, this advisory recommends reducing sulfate concentrations to or below 250 mg/L, the EPA's Secondary Maximum Contaminant Level (SMCL) for sulfate. The SMCL is based on taste considerations. It is not a federally enforceable regulation, but is intended as a guideline for States. States may establish higher or lower levels depending on the local conditions, such as unavailability of alternate source waters or other compelling factors, provided that public health and welfare are not adversely affected.

A health-based advisory for acute effects (absence of laxative effects) of 500 mg of sulfate/L is recommended. This value depends on the absence of other osmotically active materials in drinking water, which could lower the sulfate level associated with a laxative effect. Where the water contains high concentrations of total dissolved solids and/or other osmotically active ions, laxative-like effects may occur if the water is mixed with concentrated infant formula or a powdered nutritional supplement. In such situations, an alternate low-mineral-content water source is advised. Infants are more susceptible than adults to diarrheal water loss because of differences in gastrointestinal structure and function.

The soft stool or diarrhea that results from sulfate is an osmotic diarrhea; that is, it happens when the osmolality (number of dissolved particles) in the intestinal contents exceeds that of the body fluids. When this occurs, water is drawn from the body fluids into the intestines, increasing the moisture content and volume of the fecal matter. Whether or not diarrhea or soft stools occur depends on the amount of sulfate and other osmotically active materials that are present in the intestines; these materials include magnesium, sodium, and some sugars. An osmotic-induced diarrhea ceases once the osmotically active gastrointestinal contents are excreted. In the case of sulfate, adults appear to adapt within 1 or 2 weeks and are no longer affected by the sulfate in their drinking water supply. Infants, however, may be more sensitive.

Sulfate in the Environment

Sulfates are naturally occurring substances that are found in minerals, soil, and rocks. They are present in ambient air, groundwater, plants, and food. The principal commercial use of sulfate is in the chemical industry. Sulfates are discharged into water in industrial wastes and through atmospheric deposition. Sulfate concentration in seawater is about 2,700 milligrams per liter

(mg/L). It ranges from 3 to 30 mg/L in most freshwater supplies, although much higher concentrations (≥ 1000 mg/L) are found in some geographic locations. In the United States, the median concentration for a 20-State cross-section was 24 mg/L; the 99th percentile value was 560 mg/L. In general, food is the principal source of exposure. However, in areas with high sulfate concentrations, exposure from water can exceed that from food.

Studies of Sulfate Effects

Long-term and short-term exposure studies to determine a hazard assessment for sulfate are currently available in humans and animals. The findings from cancer, noncancer, and taste and odor studies are discussed below.

Cancer Studies. There has been no traditional NTP oral cancer bioassay for inorganic sulfate as the ion of interest. In an 8-month preliminary study, no tumors were observed in Wistar rats after intramuscular injection of 0.7 mg sodium sulfate every other day for 4 weeks. However, in this study the sodium sulfate treatment was used as a control against which to evaluate the effects of nickel sulfate and nickel hydroxide. Accordingly, the present database is of limited value for evaluating the tumorigenicity of sulfate. After reviewing toxicity data on sulfates food additives, the Select Committee of the Life Sciences Research Office concluded that there was no evidence that sulfuric acid or ammonium, calcium, potassium, and sodium sulfates present a hazard to the public health when they are used at levels that are current or that might reasonably be expected in the future.

Noncancer Studies. The collective evaluation of the noncancer data in humans and animals suggests that acute exposures to sulfate exert a laxative effect (loose stool) and sometimes diarrhea (unusually frequent or unusually liquid bowel movements) following acute exposures to high concentrations. However, these effects are not observed for longer term exposures. This may be because of acclimation to sulfate over time.

No adverse developmental effects were observed following the administration of 2,800 mg/kg/day of sulfate to pregnant ICR/SIM mice on gestation days 8 to 12. No reproductive effects were observed following the ingestion of drinking water containing up to 5,000 mg/L of sulfates by ICR/SIM mice and 3,298 mg/L of sulfates by Hampshire × Yorkshire × Duroc pigs . On the basis of these studies, sulfate does not appear to be a reproductive or a developmental toxicant.

Studies on Taste and Odor. Few studies are available that report on the organoleptic properties (i.e., taste and odor) of sulfate. None of the studies reported an odor threshold; therefore, all of the reported values are based on taste thresholds. It is not possible to precisely identify a specific taste threshold for sulfates in drinking water because the taste threshold concentration varies among individuals. In addition, the associated cations, different water matrices, and temperatures also influence taste. On the basis of the available data, no significant taste effects have been found to occur at sulfate concentrations of about 200–300 mg/L.

Characterization Summary

The data from short-term studies suggest that a mild laxative response can occur at sulfate concentrations greater than 500 mg/L, especially if there are other osmotically active substances present in the water. In the absence of other osmotically active materials, the laxative effects are unlikely to be observed at concentrations up to about 1,000 mg/L sulfate. These effects are exhibited as an increase in stool volume, moisture, and/or increased intestinal transit time rather than frank diarrhea.

Where drinking water contains high levels of sulfate or total dissolved solids, it should not be used in the preparation of powdered infant formula or nutritional supplements. An alternate low-mineral water source should be used. Because laxative effects have not been observed with long-term exposures to sulfate-containing water, the data suggest that acclimatization occurs as exposures continue.

The available database does not permit EPA to construct a quantitative dose-response assessment for the laxative effects of sulfate. The current SMCL of 250 mg/L should protect almost all consumers from the esthetic effects of sulfate, and the health-based advisory value of 500 mg/L will protect against sulfate's laxative effects in the absence of high concentrations of other osmotically active chemicals in the water.

1.0 INTRODUCTION

This advisory provides information to Tribes, States, local drinking water facilities, and public health personnel on the health and taste effects resulting from sulfate contamination of potable water. There are limited scientific data on the health effects of sulfate, but adequate data are available on the range of exposure concentrations that may pose a concern.

2.0 SULFATE IN THE ENVIRONMENT

Sulfates occur naturally and are abundant in the environment, generally originating from mineral deposits, soil, and rocks, or the combustion of sulfur-containing fuels. Sulfate, a soluble, divalent anion (SO_4^{2-}), results from the oxidation of elemental sulfur, sulfide minerals, or organic sulfur (Alley 1993, Field 1972, Wetzel 1983). The anion is often associated with alkali, alkaline earth, or transition metals through ionic bonds (Field 1972).

Sulfates are used in mining, pulping, metal and plating industries, water and sewage treatment, and leather processing, and in the manufacture of numerous chemicals, dyes, glass, paper, soaps, textiles, fungicides, insecticides, astringents, and emetics (Greenwood et al. 1984). Various sulfate salts are used in foods (FDA 1999), and ammonium sulfate is used in the fertilizer industry.

Sulfur is the 14th most abundant element in the earth's crust, and the 8th or 9th most abundant in sediments (Kaplan 1972). It is constantly transferred among compartments by the sulfur cycle and is ubiquitous in the environment. Anthropogenic sulfur emissions have a significant impact on the sulfur cycle, with at least 80% of global sulfur dioxide (SO_2) emissions and more than 45% of river-borne sulfates traceable to human activity (Moore 1991).

2.1 Water

Sulfate is found almost universally in natural waters at concentrations ranging from a few tenths to several thousand milligrams/liter (mg/L). The highest concentrations are usually found in groundwater and are considered to be a mixture of sulfates from atmospheric, geochemical, and biological sources. Approximately 30% of sulfate in groundwater may be of atmospheric origin, and the remainder from geologic and biological processes. Sulfates are discharged into surface water through industrial wastes and atmospheric deposition of sulfur dioxide.

The sulfate concentration in seawater is about 2,700 mg/L (Hitchcock 1975) and ranges from 3 to 30 mg/L in freshwater lakes (Katz 1977). Sulfate content in drinking water ranges from 0 to 1,000 mg/L in the United States (Trembaczowski 1991). In a survey of rivers in western Canada, sulfate concentrations ranged from 1 to 3,040 mg/L, with concentrations generally in the range of 1 to 580 mg/L (Environment Canada 1984).

Sulfate has been monitored under the Safe Drinking Water Act (SDWA) Unregulated Contaminant Monitoring (UCM) program since 1993 (57 FR 31776). Monitoring ceased for small public water systems (PWSs) under a direct final rule published January 8, 1999 (64 FR

1494), and ended for large PWSs with promulgation of the new Unregulated Contaminant Monitoring Regulation (UCMR) issued September 17, 1999 (64 FR 50556) and effective January 1, 2001.

The Safe Drinking Water Information System (SDWIS/FED) is a database of analytical data on the concentrations of contaminants in drinking water. Sulfate levels reported in the SDWIS/FED database were analyzed from a 20-State cross-section (U.S. EPA 2001). The median concentration of all PWS samples was 24 mg/L and the 99th percentile concentration of all PWS samples was 560 mg/L. Minimum reporting levels varied from system to system and State to State. The 99th percentile concentration is a summary statistic to indicate the upper bound of occurrence values because maximum values can be extreme values (outliers) that sometimes result from sampling or reporting error.

Additional sulfate occurrence data submitted for EPA's Chemical Monitoring Reform (CMR) evaluation by the States of Alabama, California, Illinois, Montana, New Jersey, and Oregon augment the SDWIS/FED 20-State cross-section analysis (U.S. EPA 2001). Five of these CMR States are not represented in the cross-section. Data from the CMR States show that concentrations are generally similar to those found in the 20-State cross-section (Table 1). Even in states such as Montana, where the 99th percentile concentration is substantially greater than that of the 20-State cross-section, the median concentration is still quite similar to the median of the cross-section States (U.S. EPA 2001).

Table 1. Median and 99th percentile concentrations for sulfate in CMR States

State	Median concentration	99th percentile concentration
Alabama	8.1 mg/L	72 mg/L
California	33 mg/L	523 mg/L
Illinois	60 mg/L	760 mg/L
Montana	22 mg/L	1,200 mg/L
New Jersey	15.9 mg/L	260 mg/L
Oregon	5.1 mg/L	79 mg/L

Although 88% of the 16,495 systems included in the 20-State cross-section reported sulfate at concentrations greater than the minimum reporting level, only about 5% exceeded the 250 mg/L SMCL. Within the twenty individual States, the number of systems that exceeded the SMCL ranged from 0 to approximately 11%. A greater percentage of surface water systems exceeded the 250 mg/L threshold; however, groundwater systems do generally show the highest sulfate concentrations (U.S. EPA 2001).

A survey of more than 900 community water supplies found that 25 (~3%) had sulfate concentrations above 250 mg/L (McCabe et al. 1970). Another survey of approximately 650 rural water systems reported sulfate present in 271 of 495 groundwater supplies (55%), with a mean sulfate concentration of 98 mg/L (a range of 10 to 1,000 mg/L). Sulfate was found in 101 of 154 surface water supplies at a mean concentration of 53 mg/L for those systems that detected sulfate (a range of 15 to 321 mg/L) (U.S. EPA 1994).

Several surveys have been conducted in Canada on the occurrence of sulfates in drinking water. A study of 17 drinking water supplies in Ontario from 1985 through 1986 found mean sulfate concentrations of 22.5 and 12.5 mg/L in treated and untreated water, respectively (Ontario Ministry of the Environment 1987). A study of 78 municipal drinking water supplies in Nova Scotia between 1987 and 1988 found mean sulfate concentrations of 14.2 mg/L in treated water (Nova Scotia Department of Public Health 1988). Sulfate concentrations were significantly higher in Saskatchewan, with median concentrations of 368 and 97 mg/L (range of 3 to 2,170 mg/L) reported for treated ground and surface waters, respectively (Saskatchewan Environment and Public Safety 1989). Based on the mean sulfate concentration measured in Ontario (22.5 mg/L) and an average daily water consumption of 2 L per day for an adult, the average daily intake from this source would be 45 mg. However, in areas with high sulfate levels in drinking water, such as Saskatchewan, daily sulfate intake could be more than 4,000 mg (WHO 1996).

2.2 Soil

Sulfate can be formed from the oxidation of elemental sulfur, sulfide minerals, or organic sulfur (Alley 1993, Field 1972, Wetzel 1983). It is one of the predominant anions in soil but is not highly mobile. Sulfate anion is often associated through ionic bonds with alkali, alkaline earth, or transition metals (Field 1972). Sulfur can be retained in soil through biochemical processes, such as incorporation into the soil organic pool as sulfate esters of humic material or other complex organic molecules. Sulfur can also be retained by adsorption onto soil particles, such as hydrous iron and aluminum sesquioxides. The average sulfur (total) concentration in soils in the United States is 1,600 parts per million (ppm or mg/kg; a range of <800 to 48,000 mg/kg) (Shacklette and Boerngen 1984). The determinant in soil for the adsorption of sulfate is the content of hydrous sesquioxides and organic matter. A strong correlation was found between pH and the ability to remove sulfates from soil solutions; therefore, factors affecting soil acidity would also affect sulfate retention (Patil et al. 1989).

2.3 Air

The main sources of atmospheric sulfate are sulfur oxides, which are primarily emitted to the atmosphere from sulfur-containing fuel combustion. Total global sulfur dioxide production continually increased from 1930 to 1980 (the years when data are available; Moore 1991). Global production of sulfur dioxide increased from 49×10^6 metric tons per year to 126×10^6 metric tons per year between 1930 and 1980.

Sulfur dioxide (SO_2) emissions have become a major concern for industrialized nations. Sulfur dioxide interacts with atmospheric water and oxygen to produce sulfuric acid (H_2SO_4), causing acid rain (Moore 1991, Wetzel 1983). In addition, SO_2 is converted to sulfate in the atmosphere

and deposited on soils. This can lead to the acidification of soil solutions and elevate sulfate concentrations in terrestrial waters (Drever 1988).

Limited information is available on the concentration of sulfates in ambient air. In a study consisting of 23,000 samples from 405 sites in 49 States, sulfate concentration was estimated to range from 0.5 to 228.4 μg/m^3. The median exposure concentrations (0.7 to 19.5 μg/m^3) were considered to be more representative of exposures than were the mean values. Using the upper median exposure concentration (19.5 μg/m^3) and assuming an inhalation rate of 20 m^3/day for a 70-kg adult, the daily dose due to sulfate in ambient air would be 6 μg/kg/day (Abernathy et al. 2000).

2.4 Food

In foods, sulfate is present as the salts of sodium, calcium, iron, magnesium, manganese, zinc, copper, ammonium, and potassium (FDA 1999). Sulfate salts are used in the food industry in a wide variety of products, such as dietary supplements, breads, preserved fruits and vegetables, gelatins, and puddings. The average daily intake of sulfate in food in the United States has been estimated to be 453 mg, based on data on food consumption and the reported usage of sulfates as additives (FASEB 1975). Many sulfate compounds in food are "Generally Regarded as Safe" (GRAS) by the U.S. Food and Drug Administration (FDA 1999).

2.5 Summary

Average daily intake of sulfate from drinking water, air, and food is approximately 500 mg, with food being the major source. However, in areas with high sulfate concentrations in the drinking water supplies, drinking water may constitute the principal intake source (WHO 1996).

3.0 CHEMICAL AND PHYSICAL PROPERTIES

Sulfate (SO_4^{2-}) is a soluble, divalent anion; common salts include sodium, potassium, magnesium, calcium, and barium sulfate. The majority of sulfate salts are soluble in water, the exceptions being the sulfates of lead, barium, and strontium. The chemical and physical properties for the common sulfate salts are detailed in Table 2 (NIOSH 1981, Budavari 1996, Scofield and Hsieh 1983).

Table 2. Chemical and physical properties of sulfates

Chemical Name	Sulfuric acid	Sodium sulfate	Potassium sulfate	Magnesium sulfate	Calcium sulfate	Barium sulfate
Chemical formula	H_2SO_4	Na_2SO_4	K_2SO_4	$MgSO_4$	$CaSO_4$	$BaSO_4$
CAS No.	7664-93-9	7757-82-6	7778-80-5	7487-88-9	7778-18-9	7727-43-7
Synonym	Oil of vitriol; Hydrogen sulfate	Thenardite (decahydrate is Glauber's salt)	*Tartarus vitriolatus; Arcanum duplicatum*	Bitter salts; heptahydrate; epsom salts	Anhydrite; Anhydrous gypsum; Anhydrous calcium sulfate	Barite; Blanc fixe; Raybar
Molecular weight	98.08	142.06	174.26	120.38	136.14	233.39
Physical state	Colorless to dark brown, oily, odorless liquid	White powder or orthorhombic bipyramidal crystals	Colorless or white rhombic or hexagonal crystals	Colorless rhombic bitter crystal	Orthorhomic crystal of variable color	Fine, heavy, odorless powder or polymorphous crystals
Boiling point (°C)	315 - 338	NA	1,689	NA	1,193	1,149
Melting point (°C)	10.4	888	1,067	NA	1,450	1,580
Density (g/mL)	1.84	2.68	2.66	2.66	2.96	4.2 - 4.5
Vapor pressure (mmHg)	< 0.001	NA	NA	NA	NA	NA
Specific gravity	1.84	2.68	2.66	1.67	2.96	4.2 - 4.5
Water solubility (g/100 mL)	Miscible	29l	12	71 at 20°C and 91 at 40°C	0.2	Practically insoluble, 0.00025
Taste threshold in water (mg/L)	NA	180 - 550	NA	400 - 600	250 - 900	NA
Odor threshold (air) (mg/m^3)	>1	NA	NA	NA	NA	NA

NA - Not available.

4.0 TOXICOKINETICS

4.1 Absorption

Estimates of sulfate absorption are derived indirectly from reported excretion data. Absorption of sulfate from the intestine depends upon the amount of sulfate ingested. For example, Bauer (1976) reported that when radiotracer doses of 60-80 μCi ^{35}S-sodium sulfate were administered orally to humans (eight adults), 80% or more of the radioactivity was recovered in the urine at 24 hours, suggesting that at least 80% of sulfate must have been absorbed. However, the high doses of sulfate that induced catharsis exceeded intestinal absorption capacity, and thus were excreted in the feces.

The type of cation associated with sulfate may also influence absorption. Morris and Levy (1983b) reported 30.2 ± 17.2% of the dose was excreted in 24-hour urine after oral administration of magnesium sulfate (5.4 g sulfate) to seven healthy individuals, as compared to 43.5 ± 12.0% excreted after oral administration of sodium sulfate (5.4 g sulfate) in five healthy men (Cocchetto and Levy 1981). This finding suggests that magnesium sulfate is absorbed to a lesser extent than sodium sulfate. Morris and Levy (1983b) indicated that the comparison of these two salts is limited in that data were obtained in separate experiments from a small number of subjects rather than from parallel experiments with the same pool of subjects.

Florin et al. (1991) performed sulfate balance studies in normal subjects and subjects with ileostomies (subjects with ileum removed surgically). The study authors wanted to determine how much sulfate reached the colon and the extent to which diet and endogenous sources contributed to colonic sulfate concentration. All subjects were fed diets containing between 1.6 and 16.6 mmol SO_4/day (0.15-1.6 g/day). Sulfate was measured in the diet, urine, and feces to determine sulfate balance (using anion exchange chromatography). There was a net absorption of sulfate with a plateau at 0.48 g/day in the ileostomy patients. Sulfate absorption in normal subjects did not plateau even at the highest dietary concentration examined. The dietary contribution to the colonic sulfate pool was determined to be up to 0.86 g/day because linearity was observed between diet and upper gastrointestinal loss for intakes greater than 0.67 g/day. The study authors concluded that diet and intestinal absorption were the principal factors affecting the amount of sulfate reaching the colon. This study also suggests that the upper digestive tract is primarily responsible for sulfate absorption.

4.2 Distribution

Inorganic sulfate is freely distributed in blood and does not accumulate in tissues. Most sulfate found in human tissues is biosynthetically incorporated into macromolecules and is organic. The normal serum level of sulfate found in humans (0.3 mmol/L or 29 mg/L) is lower than that in rodents (1 mmol/L or 96 mg/L) or in other animal species (Krijgsheld et al. 1980, Cole and Scriver 1980).

A circadian variation of serum inorganic sulfate levels has been demonstrated in humans. Hoffman et al. (1990) fed seven male volunteers an identical diet, including fluids, a parameter that is not typically included in dietary studies. Blood samples were collected in a total of 10 intervals over a 24-hour period. Average serum inorganic sulfate levels were lowest in the

morning (302 μmol/L or 29 mg/L) and highest in the early evening (408 μmol/L or 39 mg/L). This difference is statistically significant ($p < 0.005$). The average 24-hour level was 360 μmol/L, or 35 mg/L. There was considerable variability among subjects. The authors speculated that a portion of the variation in serum sulfate could be due to variation in the dietary sulfate content.

It is reported that dietary protein could have major influence on the serum sulfate levels. For example, Cole et al. (1991) studied 12 fasting subjects who were randomly fed an isocaloric meal containing either high or low protein content and monitored their serum sulfate levels up to 3.5 hours after feeding. Serum sulfate levels increased from a baseline value of 276 to 314 μmol/L (27 to 30 mg/L) at 2.5 hours after the low-protein meal and returned to the baseline by 3.5 hours. Serum sulfate levels increased from baseline values of 253 to 382 μmol/L (24 to 37 mg/L) at 3 hours and remained significantly elevated at 3.5 hours after the high-protein meal. The increase in inorganic sulfate was attributed to the oxidation of sulfur containing amino acids. The reason for the differences in the time to reach peak sulfate levels between the low- and high-protein groups is not clear. The inorganic sulfate excreted in the urine was not measured in this study.

Ingesting drinking water containing high sulfate concentrations has only slight effects on serum sulfate levels. Hindmarsh et al. (1991) compared serum levels of inorganic sulfate in 14 healthy volunteers at 2 locations (Saskatoon: 8 men; Rosetown: 4 men and 2 women) using municipal drinking water with varying sulfate concentrations. In Saskatoon the sulfate concentration was 77 ppm (mg/L) and in Rosetown the sulfate concentration was 1,157 ppm (mg/L). The cations associated with the sulfate were not reported. Baseline serum levels of inorganic sulfate were 0.35 ± 0.06 mmol/L (34 mg/L) in the Saskatoon subjects and 0.50 ± 0.11 mmol/L (48 mg/L) in the Rosetown subjects. These findings suggest that a 15-fold increase in sulfate concentration in drinking water will result in only a 1.4-fold increase in serum sulfate. The reasons for observing only a slight increase in serum sulfate in Rosetown subjects could be homoeostatic control mechanisms and dietary differences.

Serum inorganic sulfate concentrations are reported to be higher in infants and young children than in adults. For example, Cole and Scriver (1980) compared serum inorganic sulfate concentrations in subjects under 3 years old (n = 46), children between 3 and 4 years old (n = 27), adolescents in a hospitalized population (10 to 18 years old) (n = 12), and healthy adults (n = 10). On the first day of life, mean sulfate concentrations were 0.47 mmol/L (45 mg/L) (95% confidence limits of 0.29 to 0.95 mmol/L), and by 3 years of age, concentrations dropped to 0.33 mmol/L or 32 mg/L, (95% confidence limits of 0.22 to 0.67 mmol/L), which was comparable to the adult levels 0.33 mmol/L or 32 mg/L (95% confidence limits of 0.22–0.43 mmol/L). The study authors state that the increased concentration in newborns might be a result of lower glomerular filtration rates, increased resorption, and/or developmental needs.

Serum levels of inorganic sulfate were found to be increased in pregnant women in the third trimester (0.434 ± 0.006 mmol/L [42 mg/L] compared to a nonpregnant control value of 0.328 ± 0.010 mmol/L [31 mg/L]) (Cole et al. 1985). It was suggested that the fetus may need to concentrate inorganic sulfate to support its development. Similarly, Cole et al. (1992) reported that inorganic sulfate levels in amniotic fluid were increased in the third trimester compared with the second trimester. Levels in amniotic fluid were 0.317 ± 0.022 mmol/L (30 mg/L) in the

second trimester, but were 0.693 ± 0.042 mmol/L (66 mg/L) in the third trimester. The sulfate levels correlated with the creatinine and uric acid levels in the amniotic fluid, suggesting that renal excretion by the fetus may be the major source of the inorganic sulfate in the amniotic fluid in the late stages of gestation.

Levels of inorganic sulfate in the cerebrospinal fluid (CSF) were reportedly lower than those in serum. Cole et al. (1982) measured inorganic sulfate in CSF from 25 infants and children. Mean CSF sulfate was 0.170 mmol/L (16.3 mg/L) in children less than 3 years of age and 0.095 mmol/L (9.1 mg/L; range 0.059 to 0.165 mmol/L) in children older than 3 years of age. Similar to CSF concentrations, the serum sulfate concentration decreased from 0.5 mmol/L (48 mg/L) in the newborn to 0.3 mmol/L (29 mg/L) in children older than 3 years of age. Because both CSF and serum sulfate levels decrease in a similar fashion, the ratio of sulfate CSF/serum remains constant at 0.33 in infants and children.

The levels of inorganic sulfate in human colostrum and milk were 0.066 ± 0.021 mmol/L (6.3 mg/L) and 0.029 ± 0.006 mmol/L (2.8 mg/L), respectively (McNally et al. 1991). The mean sulfate level in the saliva in fasting adults (n = 17) was 0.072 ± 0.004 mmol/L, or 6.9 mg/L (Cole and Landry 1985).

4.3 Metabolism

Inorganic sulfate is incorporated into several types of biomolecules, such as glycoproteins, glycosaminoglycans, and glycolipids (Brown et al. 1965, Daughaday 1971, Morris and Sagawa 2000). Inorganic sulfate enters a metabolic pathway as an activated nucleotide intermediate, 3′-phosphoadenosine-5′-phosphosulfate (PAPS), which serves as a substrate for a number of relatively specific sulfotransferases. Sulfotransferases are enzymes that catalyze the sulfation process (or sulfamation in the case of aromatic amines). They are found in the intestinal mucosa, liver, and kidney (Bostrom 1965, Mulder and Keulemans 1978) and in human platelets (Rein et al. 1981). Sulfate plays an important role in the detoxification and catabolism of various endogenous (catecholamines, steroids, bile acids) and exogenous (acetaminophen and other drugs) compounds. Sulfate combines with several of these compounds to form soluble sulfate esters (Mulder and Keulemans 1978, Weitering et al. 1979, Sipes and Gandolfi 1991).

Because inorganic sulfate is used in the metabolism of several compounds, sulfate levels could be affected by the presence of drugs in the body. In humans, the effect of acetaminophen administration on the serum sulfate pool has been studied (Morris and Levy 1983a). In eight human volunteers orally administered 1.5 g of acetaminophen, the mean serum concentration of inorganic sulfate was significantly ($p < 0.001$) reduced from 0.410 to 0.311 mmol/L (39 to 30 mg/L) within 2 hours. Similar findings were observed in other human studies (Hendrix-Treacy et al. 1986), as well as in animals (Morris et al. 1984), after acetaminophen administration.

4.4 Excretion

Sulfates are usually eliminated by renal excretion in free unbound form or as conjugates of various chemicals. At high sulfate doses that exceed intestinal absorption, sulfate is excreted in feces.

Cocchetto and Levy (1981) conducted a study with five male volunteers who were orally administered 18.1 g $Na_2SO_4 \cdot 10H_2O$ (5.4 g sulfate) in 50 mL of water as a single bolus dose or as four equally divided hourly doses. Urinary excretion of inorganic sulfate was measured at 24, 48, and 72 hours. Prior to dosing, the baseline excretion of inorganic sulfate (free form) was measured several times for each individual. The normal baseline excretion of inorganic sulfate ranged from 13 to 25 mmol/24 hours (1.3 to 2.4 g/24 hours). To calculate the amount of the exogenous dose that was excreted, the individual baseline values were subtracted from the total urinary inorganic sulfate. Over 72 hours, a mean of 53.4% of the single dose or 61.8% of the divided dose was recovered in the urine. In general, at least two-thirds of the 72-hour sulfate excreted appeared in the urine in 24 hours. The divided dose was fairly well tolerated, but the single dose caused severe diarrhea.

The excretion of inorganic sulfate in humans is dependent on the cation. Morris and Levy (1983b) reported that orally administered magnesium sulfate in humans was absorbed less completely and more variably than sodium sulfate. Seven male volunteers received 13.9 g of $MgSO_4 \cdot 7H_2O$ (5.4 g sulfate) in four 1.4-g portions in 100 mL of water over a 4-hour period. Based on the concentration of free sulfate in 72-hour urine, at least 37% of the dose was excreted. An average of 30.2% ± 17% of the sulfate was excreted in urine over 24 hours for magnesium sulfate as compared with 43.5% ± 12% for sodium sulfate. There was high intersubject variation. Compared to sodium sulfate administered in an identical fashion, the magnesium salt was less bioavailable.

Bauer (1976) reported that when doses between 60 and 80 μCi ^{35}S (as sodium sulfate) were administered orally to eight humans, 80% was recovered in the urine at 24 hours. For comparison, 86% of the same dose given intravenously was excreted in the urine in 24 hours.

The kidney regulates and maintains serum sulfate levels through a capacity-limited reabsorption mechanism. In humans, the maximum rate of transport is 0.11 mM/min. If intestinal absorption is slow or saturated, sulfates are eliminated in the feces. As a result, sulfates do not accumulate in the body even after consumption of high levels (Morris and Levy 1983a, Cole and Scriver 1980).

5.0 HEALTH EFFECTS DATA

Data are available on the short- and long-term effects of sulfate in humans and animals. In general, a laxative effect is the most common manifestation of exposure to high concentrations of sulfate. The soft stool or diarrhea that results from sulfate is an osmotic diarrhea, i.e., one that results when the osmolality of the intestinal contents exceeds that of the interstitial fluids. When this occurs, water is drawn across the intestinal membrane into the lumen, increasing the moisture content and volume of the fecal matter. This leads to an increased intestinal peristalsis and evacuation of the intestinal contents. Poorly absorbed dissolved materials such as magnesium sulfate, sorbitol, or lactulose are often associated with osmotic-induced diarrheas. An osmotic-induced diarrhea ceases once the osmotically active gastrointestinal contents are excreted (Stipanuk 2000).

The osmotic diarrheal response to sulfate is influenced by the total temporal osmolyte load, as

well as the sulfate concentration. For example, if water contains magnesium ion as well as sulfate ion, the diarrheal response will be increased because both ions are osmotically active. This complicates interpretations of some of the ecological sulfate studies where data are reported for sulfate concentrations but not for the presence of other drinking water constituents that may be osmotically active.

5.1 Human

5.1.1 Short-Term Exposure Studies

Sulfate salts are known to have laxative properties in humans (Schofield and Hsieh 1983). A dose of 15 g of magnesium or sodium sulfate will produce catharsis within 3 hours, but lower doses can also produce this effect. For example, approximately 5 g of magnesium sulfate was reported to cause significant laxative effects when administered in a dilute solution to a fasting man (Fingl 1980). Cocchetto and Levy (1981) reported that a single dose of 8 g of anhydrous sodium sulfate induced severe diarrhea lasting up to 24 hours in five human subjects. However, the same amount of sodium sulfate taken at four equal hourly doses produced either no diarrhea or mild diarrhea of short duration.

Humans appear to develop a tolerance to water containing high sulfate concentrations (Schofield and Hsieh 1983). Although the rate at which acclimation occurs has not been determined, it is generally considered to occur in adults within one to two weeks (U.S. EPA 1999b). No specific data on the length of time necessary for humans to acclimatize to the cathartic effects of sulfates were identified.

The sulfate salt is important in determining the extent and nature of any laxative effect. Morris and Levy (1983b) reported that when humans were given the same millimolar dose of sulfate as either magnesium or sodium sulfate, the magnesium sulfate induced more adverse effects, ranging from upset stomach to diarrhea, than did sodium sulfate.

Chien et al. (1968) reported three cases of diarrhea in infants in Saskatchewan, Canada, attributable to exposure to high sulfate concentrations in the water supply. In each case, local well water with sulfate concentrations between 630 and 1,150 mg/L and a high total dissolved solid concentration of 2,424 to 3,123 mg/L was used to prepare infant formulas. The total dissolved solid concentrations reported in this study greatly exceeded the United States' secondary standard for total dissolved solids of 500 mg/L.

When milk or water with low sulfate content, and presumably lower total dissolved solids, replaced the local well water, recovery occurred (Chien et al. 1968). Diarrhea returned when the original well water was re-introduced. The study authors concluded that waters with a sulfate content higher than 400 mg/L were unsuitable for consumption by infants. Interpretation of this study is limited by the number of the study subjects (n = 3) and by the lack of data on sulfate concentration in and osmolarity of the infant formula.

In a case-control investigation to assess the association between infant diarrhea and ingestion of water containing elevated sulfate levels, Esteban et al. (1997) reported that no significant association existed between exposure to sulfate from tap water and subsequent diarrhea in

infants. A total of 274 mothers of infants born in 19 South Dakota counties with high sulfate concentrations in tap water were identified and interviewed using a telephone questionnaire (n = 262) or in person (n = 12). The mothers were questioned on the frequency and consistency of the infant's bowel movements and on the amount of water that the infant drank in the previous 7 days. Diarrhea was defined as three or more loose stools in a 24-hour period. A sample of the water used in the infant's diet was also submitted by the mother and analyzed for sulfate. Two hundred seventy-four infants were included in the study. Cases were defined as infants that developed diarrhea (as identified by the mothers); controls were defined as infants that did not develop diarrhea.

The average sulfate concentration in drinking water for cases was 416 mg/L versus 353 mg/L for controls. The corresponding median sulfate concentration for cases was 289 mg/L (range 0–1,271 mg/L); the median concentration for controls was 258 mg/L (range 0–2,787 mg/L). The median water intake for the controls was lower than for the cases (0.2 vs. 0.5 L/day). Mean and median daily sulfate intake from water for all infants in the study was 29 and 17 mg/kg/day, respectively. Mothers reported diarrhea in 19% of the infants living in households with sulfate levels in tap water >500 mg/L and in 14% of infants living in households with sulfate levels <500 mg/L. There was no significant correlation (OR = 1.4; 95% CI = 0.5–4.0) between the incidence of diarrhea and the level of sulfate in water samples .

Heizer et al. (1997) examined bowel function in healthy adults following exposure to various sodium sulfate concentrations in drinking water. In a single-dose study of six adults (three men and three women), each subject received drinking water with sulfate concentrations of 0 or 1,200 mg/L for two consecutive 6-day periods. A fluid intake of 36 mL/kg/day was maintained in these subjects. Stool mass, frequency, consistency, and mouth-to-anus appearance time for colored markers were measured. When subjects received sulfate at 1,200 mg/L, mean stool mass per 6-day pool period increased from 621 g to 922 g (p = 0.03). Mean stool mass per hour increased from 4.8 g to 6.6 g (p = 0.03) with a change in sulfate concentration from 0 to 1,200 mg/L. However, stool frequency, consistency, and mouth-to-anus appearance time were not significantly different for the high-sulfate water.

Heizer et al. (1997) also reported data from a multiple dose study in four subjects (two men and two women). Each subject received drinking water with increasing sulfate concentrations of 0, 400, 600, 800, 1,000, and 1,200 mg/L over six consecutive 2-day periods. In this study, there was a significant linear trend for decreasing mouth-to-anus marker appearance time with increasing sulfate concentrations (p = 0.03). When the 10 subjects (4 subjects from the multiple-dose study and 6 subjects from the single-dose study reported above) were used to compare effects of 0 mg/L and 1,200 mg/L sulfate, significant differences in stool consistency (p = 0.02) and transit time (p = 0.03) were observed. However, none of the subjects reported diarrhea or passed more than three stools per day.

In order to determine the effects of high sulfate concentrations in transient populations (students, visitors, hunters, etc.), the Centers for Disease Control (CDC), with funding from EPA (1999a), conducted a study in adult human volunteers. The study was designed to determine if any adverse effects would occur in persons suddenly changing drinking water sources from one with little or no sulfate to one with high sulfate concentrations. A total of 105 participants were randomly assigned to five sulfate-exposure groups and were exposed to sulfate in bottled water

over a period of 6 days. The participants received water containing sulfate only for days 3 through 5 and were given sulfate-free bottled water for days 1, 2, and 6. Subjects were blinded to the level of sulfate in the drinking water. The number of participants in each exposure category varied: 0 mg/L (n = 24), 250 mg/L (n = 10), 500 mg/L (n = 10), 800 mg/L (n = 33), or 1,200 mg/L (n = 28).

Several criteria were used to monitor whether the sulfate had a laxative effect. The subjects kept track of the number of bowel movements they had on each day of the study. They were also asked to rate the quality of their stools according to three definitions of diarrhea. Osmotic diarrhea was defined as an increase in stool volume, diarrhea 1 was defined as paste-like or liquid stools, and diarrhea 2 was defined as change in stool bulk and consistency. There were no statistically significant differences in the mean number of bowel movements among the groups on days 3, 4, 5, or 6; or in the mean number of bowel movements when days 3, 4, and 5 were compared with days 1 and 2. There was also no apparent trend in the percentage of subjects that reported diarrhea during the exposure period as opposed to the control period (days 1 and 2) using any of the definitions of diarrhea.

The data were also evaluated using logistic regression analysis to determine the effects of sulfate based on dose. The dose was calculated for each subject from the amount of water consumed, the amount of sulfate in drinking water, and the body weight of the participant. Using this method, there were no statistically significant dose-response associations between sulfate dose and reports of diarrhea (one-sided $p = 0.099$) using any of the three definitions.

The authors also combined the incidence for diarrhea under any of the three definitions for the lowest three dose groups (0, 250, and 500 mg/L) and compared it with the incidences of the 800 mg/L and 1,200 mg/L dose groups. There were no statistically significant differences between groups for any of the three diarrhea categories. However, there was a dose-related trend for increased stool volume (osmotic diarrhea) with increasing sulfate exposure when the three groups were compared (9%, 15%, and 18%, respectively).

5.1.2 Long-Term Exposure Studies

Peterson (1951) analyzed the data from about 300 questionnaires that had been collected by the North Dakota Department of Health as part of its routine monitoring of the mineral content of groundwater supplies. The questionnaires had been distributed to private well owners along with requests for samples of well water for analysis. The questionnaires solicited information on odor, taste, effects on cooking, and laxative effects from the water. The questionnaires analyzed by Peterson (1951) were a subset of about 2,500 submitted to the Department of Health. They were selected because analytical data for the water were available and the questionnaire was complete enough to be used for data analysis. Peterson (1951) plotted the concentration of sodium sulfate and magnesium sulfate in the water against whether water use was associated with a laxative effect. Both sodium and magnesium ions were present in most of the water samples. He concluded that sulfate was likely to have a laxative effect when the concentrations exceed 750 mg/L, but was unlikely to have such an effect at concentrations less than 600 mg/L. As the concentration of the magnesium in the water increased, the sulfate concentration that was associated with a laxative response decreased.

Moore (1952) analyzed data from 248 wells from the North Dakota Department of Health survey (Peterson 1951 data). Questionnaires completed by the users of the wells provided a YES or NO response for laxative effects for 176 of 248 wells. For 69 wells with positive responses for laxative effects, the mean sulfate level was 1,250 mg/L and the median was 1,090 mg/L. For 107 wells with negative responses, the mean and median sulfate levels were 500 mg/L and 403 mg/L, respectively. When the data were separated into specific ranges, the percent of YES responses for laxative effects was 22% (10/46) for wells with levels between 0 and 200 mg/L; 24% (9/37) for wells with levels between 200 and 500 mg/L; 33% (13/39) for wells with levels between 500 and 1,000 mg/L; and 69% (37/54) for levels >1,000 mg/L. Moore (1952) concluded that sulfate ion concentration is critical at 1,000 mg/L and at more than 2,000 mg/L is almost certain to produce discernible physiological effects. For a combination of magnesium and sulfate, effects are likely to occur when the total concentration exceeds 1,000 mg/L. Many of the wells in this data set also contained high levels of total dissolved solids and magnesium. Similar results were obtained when Cass (1953) analyzed the data provided in the North Dakota survey.

5.2 Animal

5.2.1 Short-Term Exposure Studies

The oral LD_{50}s of ammonium sulfate, sulfuric acid, and potassium sulfate in the rat are 3,000–4,000 mg/kg, 2,140 mg/kg (FASEB 1975), and 6,600 mg/kg (RTECS 2000), respectively. The oral LD_{50} of sodium sulfate in the mouse is 5,989 mg/kg (RTECS 2000).

Adams et al. (1975) supplied groups of three White Leghorn hens with drinking water containing 250 to 16,000 mg sulfate/L (as sodium or magnesium sulfate). At 16,000 mg/L, the hens exhibited decreased body weight, decreased feed consumption, decreased egg production, and increased water consumption. At this dose, mortality (100%) occurred by day 7 for hens drinking water with magnesium sulfate, and by day 12 for hens drinking water with sodium sulfate. Necropsy revealed focal necrosis of individual renal glomeruli, with uric acid accumulation in both the kidney and gut. Similar, but less severe, histologic changes were seen in hens receiving water at 4,000 mg/L for up to 3 weeks.

Paterson et al. (1979) administered drinking water containing 3,000 mg/L of added sulfate (as either sodium sulfate or a 1:1 combination of both sodium and magnesium sulfate) for 28 days to groups of 17 or 18 weanling pigs (7.7 to 8 kg). The control group (n = 16) received water containing 320 mg/L sulfate. No significant changes ($p > 0.05$) in average daily weight gain or feed/gain ratio were observed when the treated group was compared to controls. Fluid consumption increased for both groups receiving the high concentration of sulfate in their water, and stools were soft for these animals compared with controls.

Sulfate (sodium and magnesium sulfate in combination or independently) was administered to young pigs at concentrations ranging from 600 to 1,800 mg/L in drinking water for 28 days. Weight gain, feed consumption, water consumption, feed conversion, prevalence of diarrhea, and evidence of common postweaning enteric pathogens were determined. Sulfate did not impair performance or health of pigs. However, loose and watery stools appeared to be more prevalent in the groups receiving 1,800 mg/L sulfate (both salts independently and in combination)

compared to control, 600 mg/L, and 1,200 mg/L groups (Veenhuizen et al. 1992). Similar results were observed in an earlier study by Anderson and Stothers (1978) in which groups of nine young pigs given water containing 600 mg/L total solids as sodium sulfate displayed scouring (soft stools), primarily during the first week of a 6-week experimental period.

Gomez et al. (1995) used neonatal piglets to study the effect of inorganic sulfate on bowel function. Two experiments were conducted to evaluate the effect of high levels of inorganic sulfate on the growth, feed intake, and feces consistency of piglets, and to determine the dose at which at least 50% of piglets develop an osmotic diarrhea. In each experiment, 40 pigs with an average age of 5 days were individually caged and reared with an automatic feeding device. Groups of 10 pigs were fed 1 of 4 liquid diets containing inorganic sulfate (anhydrous sodium sulfate) at 0, 1,200, 1,600, or 2,000 mg/L (of diet) for an 18-day study, or 0, 1,800, 2,000, or 2,200 mg/L for a 16-day study. The levels of added sulfate did not affect ($p > 0.05$) the growth of piglets or their feed intake. Whereas 1,200 mg sulfate/L had essentially no effect on feces consistency, concentrations greater than 1,200 mg/L increased the prevalence of diarrhea. Concentrations greater than 1,800 mg/L resulted in a persistent diarrhea. The changes in feces consistency suggest that the level of added dietary inorganic sulfate at which 50% of piglets develop diarrhea is between 1,600 and 1,800 mg/L. Analysis of rectal swabs showed no evidence of *E. coli* or rotavirus infection.

5.2.2 Long-Term Exposure Studies

In a 90-day subchronic study, Wurzner (1979) examined the effects of sulfate in drinking water in Sprague-Dawley rats (25/sex/group). Treated animals received mineral waters containing low (<10 mg/L), intermediate (280 mg/L), or high (1,595 mg/L) concentrations of sulfate. Control animals were provided with tap water containing 9 to 10 mg/L sulfate. No information was provided on the concentrations of minerals other than sulfate in the three different mineral waters. No mortalities or effects on body weight, food consumption, food efficiency (a measure of food intake versus body weight change), or water consumption were observed. No soft feces or diarrhea were observed. No effects on hematology or serum chemistry (blood urea nitrogen, glucose, triglycerides, cholesterol, total protein, and alkaline phosphatase activity) were observed after 90 days. Organ weights were not affected, and no histologic changes were observed at any tissue site. Five rats/sex/group continued treatment beyond the 90 days. Blood urea nitrogen in the high-dose group tended to be decreased in both sexes, but this occurred only after 6 months of treatment.

Digesti and Weeth (1976) supplied groups of four weanling Hereford-Angus heifers with drinking water containing 110 to 2,500 mg/L sodium sulfate. After 90 days of dosing, no overt toxicity was observed in any animals; feed consumption, water consumption, and growth were not affected. Increased levels of methemoglobin and sulfhemoglobin were observed in the animals consuming 1,250 and 2,500 mg/L sodium sulfate; this was attributed to the bacterial reduction of sulfate to sulfide in the rumen. At 2,500 mg/L, renal filtration of sulfate was increased by 37.7% and renal reabsorption was decreased by 23.7%.

5.2.3 Reproductive and Developmental Studies

Three oral studies on reproductive and developmental effects were identified for sulfate. On the basis of these studies, it appears that sulfate does not induce adverse reproductive or developmental effects.

Sodium sulfate was administered by gavage at a concentration of 2,800 mg/kg/day to pregnant ICR/SIM mice on gestation days 8 to 12 (Seidenberg et al. 1986). There was no evidence of maternal toxicity or increased resorption rate. Pup survival was 100%, and no adverse developmental effects were observed. Neonatal birth weight was significantly increased in the treated group compared with controls.

Six groups of 10 female, randomly bred albino ICR mice were administered sodium sulfate in drinking water at dose levels of 0 (distilled water control), 0 (sodium control), 625, 1,250, 2,500, or 5,000 mg/L beginning 1 week prior to breeding (Andres and Cline 1989). The amount of sodium in all groups, except the distilled water control, was kept constant by administering sodium bicarbonate. Control mice, receiving only distilled water, consumed significantly less ($p < 0.05$) than mice receiving sulfate treatments, and sodium-control mice drank significantly more water ($p < 0.05$) than mice treated with sulfate. All mice were carried to term. No differences were found in litter size, litter weaning weights, or gestational or lactational weight gain of the dams among sulfate treatments. Histopathology evaluations were not performed. The authors concluded that water containing up to 5,000 mg/L sulfate is not toxic to the gestating mouse.

Paterson et al. (1979) investigated the effects of water with a high sulfate content on swine and their offspring. The pigs, 31 sows and 27 gilts of Hampshire × Yorkshire × Duroc breeding, were randomly divided into three groups that received either tap water (320 mg sulfate/L) or water with sodium sulfate added at 1,790 mg/L or 3,298 mg/L. The animals were given access to these waters from prebreeding day 30 through lactation day 28. No significant differences in gestation or lactation weight gain, number of pigs delivered, or average pig and litter birth weights were reported.

5.2.4 Cancer Studies

In a study of the toxicity and carcinogenicity of nickel compounds (nickel hydroxide and nickel sulfate) in Wistar rats, sodium sulfate (used as a control) did not appear to be tumorigenic (Kasprazak et al. 1980). In this study, Wistar rats (100 males and 10 females) were injected intramuscularly every other day for 4 weeks with 0.7 mg sodium sulfate/rat (approximately 2 mg SO_4^{2-}/kg in aqueous solution at pH 5.6). After 8 months, no tumors were observed in either the sodium sulfate or nickel sulfate treated rats. However, the value of this study in assessing the carcinogenic effects of sulfate ingestion is limited because of the route of exposure, the duration of the study, and the nonstandard protocol.

6.0 ORGANOLEPTIC PROPERTIES

Water contaminated with sulfates may have an unpleasant taste. Characteristics such as taste, odor, and color, often referred to as organoleptic properties, are not used by EPA for developing primary water standards. Organoleptic properties, however, can be used in the establishment of secondary drinking water standards.

EPA established a secondary drinking water standard of 250 mg/L for sulfate in 1984 based on taste properties (U.S. EPA 1984). This value was adopted from the Public Health Service Drinking Water Standards (PHS 1962). Secondary standards are not enforceable by the Federal Government; they are recommended to States as reasonable goals for contaminants, but there is no obligation for the States to reach these goals.

There is a paucity of actual experimental data available on the taste threshold for sulfate. Taste threshold concentrations for several common sulfate salts have been reported. The taste thresholds varied depending on the type of salt: 170-370 mg/L sulfate as sodium sulfate, 180-640 mg/L as calcium sulfate, and 320-480 mg/L as magnesium sulfate (Lockhart et al. 1955, as cited in PHS 1962).

The detection of taste differs from the perception of a taste as unpleasant. Accordingly, the results reported by Heizer et al. (1997) on the response of 10 subjects to sulfate in drinking water are of interest. After completion of the exposure component of this study, 8 of the 10 subjects rated the taste of 1,200 mg/L sulfate, as sodium sulfate, as neutral to slightly unpleasant. One subject rated the water as moderately unpleasant and another as very unpleasant. This study indicates there is variability in the response to the taste of sulfate, and the threshold for detecting an unpleasant taste is apparently above the threshold of taste.

In the study of the laxative effects of sulfate that was conducted for EPA by CDC (U.S. EPA 1999a), the subjects were asked if the smell or taste of the water was different from that which they usually consumed. All subjects received sulfate-free control water on days 1, 2, and 6 of the study and either the sulfate-free water (controls) or a sulfate-containing water on days 3, 4, and 5 of the study. There was a definite increase in the number of subjects who thought that the water tasted differently on days 3, 4, and 5 for the 800 and 1,200 mg/L concentrations, with 79% and 82% reporting a difference in taste, respectively. Average daily water consumption also decreased in these same groups on days 3, 4, and 5 when compared with intakes on days 1, 2, and 6. About half of the participants receiving the 250 and 500 mg/L concentrations reported a difference in taste (57% and 50% respectively) on the days when they were exposed to sulfate. Water consumption showed a downward trend over this same period as well. Twenty-five percent of the control group also reported that there was a difference in the taste of the water. For this group, there was no downward trend in water consumption across the 3-day exposure period.

The ability to taste differs among individuals, as well as in the same individual at different times. Temperature and the presence of other dissolved solids in the water also influence taste. Given the expected variability in taste, as well as the results in Heizer et al. (1997), the U.S. EPA secondary maximum contaminant level (SCML) of 250 mg/L should be adequately protective for adverse sulfate taste effects.

7.0 CHARACTERIZATION OF HAZARD AND DOSE-RESPONSE

7.1 Hazard Characterization

Some data are available that report human responses to sulfate. Data include those from controlled settings (i.e., studies and experimental trials) and uncontrolled settings (i.e., case studies from areas with high sulfate concentrations in the drinking water). Most of the available data are based on short-term exposure and were obtained from controlled studies. Reports on long-term exposure are based on responses to questionnaires in North Dakota and South Dakota, States with high sulfate concentrations in their drinking water supply. In animals, data on reproductive and developmental effects are available for short-term and long-term exposures to sulfate. There are limited data on the potential carcinogenic effects of sulfate.

The available data demonstrate that sulfate induces a laxative effect following acute exposures to relatively high concentrations (Anderson and Stothers 1978, Fingl 1980, Schofield and Hsieh 1983, Stephen et al. 1991, Cochetto and Levy 1981, U.S. EPA 1999a, Gomez et al. 1995, Heizer et al. 1997). The concentrations of sulfate that induced these effects varied, but all occurred at concentrations >500 mg/L. However, the severity of the laxative effect that occurs from acute sulfate exposures may be dependent on the sulfate salt, as well as how the dose is administered. For example, magnesium sulfate exerts a stronger laxative effect than sodium sulfate. This likely occurs because magnesium sulfate is absorbed less completely than sodium sulfate and has a more pronounced effect on the osmolarity of the intestinal contents (Morris and Levy 1983b). Additionally, a single dose of sulfate that produces a laxative effect does not have the same effect when divided and administered in intervals, i.e., a single dose produced severe diarrhea, whereas divided doses produced only mild or no diarrhea (Cochetto and Levy 1981).

Chronic and subchronic exposures to high concentrations of sulfate do not appear to produce the same laxative effect as seen in acute exposures. In a 90-day study using Sprague-Dawley rats, Wurzner (1979) did not observe soft feces or diarrhea in rats administered mineral waters containing up to 1,595 mg/L of sulfate. However, earlier reports indicate that chronic exposure to high sulfate concentrations in drinking water resulted in laxative effects in humans (Peterson 1951, Moore 1952, Cass 1953). These reports used data that were based on questionnaires, which may be subject to bias. For example, the questionnaire included an inquiry about the laxative effect that requested a YES or NO response. This type of question is subject to the respondent's interpretation of what constitutes a laxative effect. In addition, sulfate was probably not the only contaminant found in the drinking water. Chronic exposure to sulfate may not have the same laxative effect as an acute exposure because humans appear to develop a tolerance to drinking water with high sulfate concentrations (Schofield and Hsieh 1983). It is not really known when this acclimation occurs; however, in adults, acclimation is thought to occur between one to two weeks (U.S. EPA 1999b).

No adverse developmental effects were observed following the administration of 2,800 mg/kg/day of sulfate to pregnant ICR/SIM mice on gestation days 8 to 12 (Seidenberg et al. 1986). No reproductive effects were observed following the ingestion of drinking water containing up to 5,000 mg/L of sulfates by ICR/SIM mice (Andres and Cline 1989) or 3,298 mg/L of sulfates by Hampshire × Yorkshire × Duroc pigs (Paterson et al. 1979). Based on these studies, sulfate does not appear to be a reproductive or a developmental toxicant.

No tumors were observed after 8 months in a study using Wistar rats injected intramuscularly with sodium sulfate every other day for 4 weeks (Kasprazak et al. 1980). Because of the short-term observation period, the route of exposure, and the experimental protocol, it is not possible to draw conclusions on the potential carcinogenicity of sulfate. Because of the limited data, U.S. EPA/Office of Water (1993) has classified sulfate as Group D–not classified as to human carcinogenicity. This category is reserved for contaminants with inadequate evidence to support a determination on carcinogenicity.

7.2 Characterization of Organoleptic Effects

The ability to taste differs among individuals, as well as for the same individual at different times. The temperature of the water, the companion ion, and the presence of other dissolved solids impact the taste sensation. There is also a difference between the concentrations that impart a taste to water and those that are classified as causing an unpleasant taste. Each of these factors makes it difficult to define a taste threshold for sulfate.

The experimental data on the organoleptic properties of sulfate in drinking water are limited. No studies were identified that were conducted using standard taste-testing procedures. In the study by Heizer et al. (1997), 8 of 10 subjects rated the taste of drinking water containing 1,200 mg/L sulfate as neutral to only slightly unpleasant. Two subjects classified the taste as moderately to extremely unpleasant. In the study conducted by CDC for EPA (1999a), about 50% of the participants could not distinguish between the taste of sulfate-free water and water containing either 250 mg/L sulfate or 500 mg/L sulfate. Even when the water contained 1,200 mg/L sulfate, 20% of the participants could not detect the taste.

Given the variability in the ability of consumers to identify a taste in water that contains sulfate, the present SMCL of 250 mg/L appears to be adequately protective of the aesthetic taste properties of drinking water containing sulfate.

7.3 Dose-Response Characterization

Although several studies (Peterson 1951, Moore 1952, Cass 1953) have examined the effects of long-term exposure of humans to sulfate in drinking water, none of them can be used to derive a dose-response characterization. These studies utilized data collected from the North Dakota Department of Health Survey (Moore 1952). An increasing trend was observed in persons reporting laxative effects as sulfate concentrations increased (i.e., 22%, 24%, 33%, and 69% for sulfate concentrations of 0-200, 200-500, 500-1,000, and >1,000 mg/L, respectively). However, the results of these studies cannot be used to derive a dose-response characterization for the following reasons: (1) the results are based on recall with little scientific weight (i.e., sulfate may have induced the laxative effects, but it cannot be proven); and (2) the water samples had varying concentrations of magnesium and total dissolved solids in addition to sulfate.

No laxative effects were observed in rats (Wurzner 1979) or heifers (Digesti and Weeth 1976) following long-term exposure to sulfate in drinking water. Consequently, these studies cannot be used for a dose-response characterization.

Because sulfate appears to exert its laxative effect with short-term exposures rather than long-term exposures, several short-term exposure studies were reviewed. Three short-term studies were identified that evaluated the effect of various sulfate concentrations on bowel function in a controlled environment: two in humans and one in animals. In the multiple-dose study by Heizer et al. (1997), sulfate concentrations of 0, 400, 600, 800, 1,000, or 1,200 mg/L were given to four subjects (two men and two women) for six consecutive 2-day periods (2 days per concentration). A significant trend was observed for a decreasing mouth-to-anus marker-appearance time of chemical markers with increasing sulfate concentration. For a single-dose study by the same researchers, six adults (three men and three women) received drinking water with sulfate concentrations of 0 or 1,200-mg/L for two consecutive 6-day periods. Statistically significant increases in mean stool mass per 6-day pool and in mean stool mass per hour were observed in the 1,200-mg/L dose group. However, none of the subjects reported frank diarrhea.

CDC conducted a study for EPA (1999a) that examined the effect of sudden changes in sulfate levels in drinking water in 105 subjects. The participants received water containing sulfate at 0, 250, 500, 800, or 1,200 mg/L from day 3 through day 5, and were given sulfate-free bottled water for days 1, 2, and 6. There were no statistically significant differences in the mean number of bowel movements in any group or a dose-response relationship between sulfate dose and reports of diarrhea (one-sided $p = 0.099$). However, when the diarrhea incidence data for the lowest three dose groups were compared to the incidence for the 800 mg/L and 1,200 mg/L dose groups, there was a dose-related trend for increased stool volume (osmotic diarrhea) when the three groups were compared (9%, 15%, and 18%). The dose-related trend, however, was not statistically significant.

Neonatal piglets were exposed to various concentrations of sulfate to simulate the effect of inorganic sulfate on the bowel function in infants (Gomez et al. 1995). No diarrhea was observed in any of the piglets at 0 and 1,200 mg/L concentrations; however, concentrations greater than 1,200 mg/L resulted in an increased prevalence of diarrhea, and concentrations greater than 1,800 mg/L resulted in persistent, nonpathogenic diarrhea.

These studies as a group suggest that there is a risk for a laxative-type response to sulfate in drinking water at concentrations greater than 1,000 mg/L (U.S. EPA 1999a, Heizer et al. 1997, Moore 1952). The observed effect is a response to the net osmolarity of the intestinal contents, and thus is influenced not only by sulfate intake, but also by the presence of other osmotically active materials in the drinking water or diet, and by the temporal pattern of sulfate ingestion. The laxative effect of sulfate can be manifest as an increase in stool mass, increased stool volume, increased stool moisture, decreased intestinal transit time, and/or frank diarrhea. Frank diarrhea did not occur in either of the controlled human studies of sulfate exposure (U.S. EPA 1999a, Heizer et al. 1997). There was merely a slight increase in stool mass or stool volume with sulfate concentrations of 800 to 1,200 mg/L.

At this time, it is not possible to characterize a dose-response relationship for laxative effects due to short- or long-term exposure to sulfate. A Centers for Disease Control and Prevention (CDC) panel favored a health advisory for situations where sulfate levels in drinking water are greater than 500 mg/L (U.S. EPA 1999b). The most sensitive endpoint was considered by the panelists to be osmotic diarrhea. The panelists concluded that the existing literature supports restricting sulfate exposure, especially for infants, when the advisory value of 500 mg/L is exceeded. The

panelists referred to the study by Chien et al. (1968), which found that sulfate levels ≥630 mg/L caused diarrhea in infants. It should be noted that this effect was observed after the infants had ingested formula made with water containing sulfate and other osmotically active agents. In fact, the total dissolved solid concentration of the water used to prepare infant formulas was high (2,424 to 3,123 mg/L) and in two cases contained substantial quantities of magnesium (124 and 130 mg/L). The CDC panel concluded that 500 mg/L seemed to be a safe level for sulfate ingestion, as 500 mg/L was shown to be safe in all studies. For comparison, the osmolarity of 500 mg/L sulfate as sodium sulfate is 15.6 mOsmol/L whereas the osmolarity of the ions (Na, K, Cl, and citrate) in Pedialyte, a preparation used to treat diarrhea and replenish electrolytes in infants, is 110 mOsmol/L. When the dissolved sugars in Pedialyte are included the osmolarity increases to 250 mOsmol/L.

The experimental data on the organoleptic properties of sulfate in drinking water are limited. In a study by Heizer et al. (1997), 8 of 10 subjects rated the taste of drinking water containing 1,200 mg/L sulfate as neutral to slightly unpleasant. Only two classified the taste as moderately to extremely unpleasant. In the study conducted by CDC for EPA (1999a), approximately 50% of the participants stated that water containing 250 mg/L sulfate and 500 mg/L sulfate tasted different from the sulfate-free control water.

Given the apparent variability in consumers' ability to identify a taste in water that contains sulfate, the present SMCL of 250 mg/L appears to be adequately protective of the esthetic taste properties of drinking water containing sulfate. The health-based advisory value of 500 mg/L will protect against sulfate's laxative effects in the absence of high concentrations of other osmotically active chemicals in the water. In situations where the water contains high concentrations of total dissolved solids and/or other osmotically active ions, laxative-like effects may occur if the water is mixed with concentrated infant formula or powdered nutritional supplements. In such situations, an alternate low-mineral-content water source is advised. Infants are more susceptible to diarrheal water loss than adults because of differences in gastrointestinal structure and function.

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