United States
Environmental Protection Agency | Office of Water 4607 | EPA 815-R-99-002 January 1999

Health Effects from Exposure to Sulfate in Drinking Water Workshop

IRBINFO# EHHEHSB979
CDC Protocol # 1779

HEALTH EFFECTS FROM EXPOSURE TO SULFATE IN DRINKING WATER WORKSHOP

Sponsored by

Centers for Disease Control and Prevention

September 28, 1998
Atlanta, Georgia

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Executive Summary

In the 1996 amendments to the Safe Drinking Water Act, Congress mandated that the U.S. Environmental Protection Agency (EPA) determine, by August 2001, whether to regulate sulfate in drinking water. If EPA decides to regulate sulfate, the agency must propose the Maximum Contaminant Level (MCL) by August 2003 and issue a final standard by February 2005. Congress also directed EPA to conduct a study with the Centers for Disease Control and Prevention (CDC) to establish a reliable dose-response relationship for health effects from exposure to sulfate and to examine effects in sensitive subpopulations (infants and transients). The directive indicated that the study must "be based on the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices," "be conducted in consultation with interested States," and be completed by February 1999.

CDC researchers had to cancel a planned community-based study of the frequency of diarrhea in infants exposed to varying levels of sulfate naturally occurring in drinking water because they could not identify a sufficiently large group of exposed infants. CDC did not find an association between exposure to sulfate in drinking water and diarrhea in adult volunteers. As a supplement to their studies and literature review, CDC and EPA organized a workshop to review CDC's sulfate studies and discuss the most relevant scientific literature examining the health effects from exposure to sulfate in drinking water.

The workshop began with presentations. Dr. Charles Abernathy, from the EPA Office of Water, presented the results of selected studies on the health effects of sulfate, a regulatory history of sulfate, a time line of the actions EPA has taken on sulfate, and an estimate of the types and numbers of drinking water systems that would be affected by the regulation of sulfate in drinking water.

There were three presentations describing the biochemistry and physiology of sulfate absorption and excretion. Dr. David Cole, of the University of Toronto, presented information on the importance of sulfate as a component of membranes and many compounds in humans, the medical effects of sulfate deficiency, and how membrane transport and regulation contribute to sulfate homeostasis. Dr. Marie Cassidy, of George Washington University, presented information on intestinal physiology, including osmotic and bacterial diarrhea, and reasons why elderly people may be susceptible to diarrhea. Dr. Marilyn Morris, of the State University of New York (SUNY)-Buffalo, discussed the transport mechanisms used in the body to regulate inorganic sulfate levels and the relative importance of the different mechanisms at different developmental stages. Dr. Guillermo Gomez, of North Carolina State University, presented a study on the gastrointestinal effects of sulfate in drinking water, using neonatal pigs as an animal model for human infants.

Dr. Lorraine Backer, of the National Center for Environmental Health at CDC, presented the results of recent studies conducted by CDC of the human health effects in

sensitive subpopulations (infants and transients) of exposure to sulfate in drinking water. The planned study of health effects in infants from exposure to sulfate in drinking water was not completed because very few mothers of newborns in the areas where there were high levels of sulfate in the drinking water provided by public water systems gave or were planning to give infant formula mixed with tap water to their babies. The study of transients involved analyzing the frequency of self-reported diarrhea in adults exposed to varying levels of sulfate in drinking water provided to them. In the adult study, there was no statistically significant association between the concentration of sulfate in the drinking water and the frequency of diarrhea. Esteban et al. (1997) found no significant association between sulfate intake and diarrhea in infants in South Dakota.

After the presentations, Dr. Carl Shy of the University of North Carolina lead the workshop participants in a discussion of four issues:

Issue 1 Do reported studies suggest that a certain sulfate level would not be likely to cause adverse effects (e.g., diarrhea in infants and travelers)?

Existing data do not identify the level of sulfate in drinking water that would be unlikely to cause adverse human health effects. The panel members noted that the available published literature included reports that piglets in experimental feeding trials and some people experience a laxative effect when consuming tap water containing from 1,000 to 1,200 mg/L of sulfate (as sodium sulfate). However, none of the studies found an increase in diarrhea, dehydration, or weight loss.

Issue 2 Does the literature support acclimatization or adaptation (what process and time frame does it take)?

Based on biologic plausibility and anecdotal reports, evidence indicates that people acclimate to the presence of sulfate in drinking water. In addition, serum sulfate levels are high (compared to adults) in human fetuses and neonates (to support rapid growth and development). However, data describing acclimation and the changes in sulfate metabolism during growth and development are limited.

Issue 3 Can an infant study be done for dose-response anywhere in the U.S. or Canada?

The difficulty of locating a population of women feeding their infants formula mixed with unfiltered tap water containing high levels of sulfate hinders the completion of a dose-response study in infants. A study using neonatal pigs could assess a dose response for both magnesium and sodium sulfates.

Issue 4 Is there enough scientific evidence that there are adverse health effects from sulfate in drinking water to support regulation? [Congress directed EPA to use the best available science to set drinking water goals and regulations.]

There is not enough scientific evidence on which to base a regulation, but panelists favored a health advisory in places where drinking water has sulfate levels of $\geq$ 500 mg/L.

Introduction

In the 1996 amendments to the Safe Drinking Water Act, Congress mandated that the U.S. Environmental Protection Agency (EPA) determine by August 2001 whether to regulate sulfate levels in drinking water. If EPA decides to regulate sulfate, the agency must propose the Maximum Contaminant Level (MCL) by August 2003 and issue a final standard by February 2005. Congress also directed EPA to conduct a study with the Centers for Disease Control and Prevention (CDC) to establish a reliable dose-response relationship for sulfate and examine effects in sensitive subpopulations (infants and transients). The directive indicated that the study must "be based on the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices," "be conducted in consultation with interested States," and be completed by February 1999.

CDC researchers had to cancel a planned community-based study of the frequency of diarrhea in infants exposed to varying levels of sulfate in drinking water because they could not identify a sufficiently large group of exposed infants. A study of adults exposed to varying levels of sulfate in drinking water provided to them did not find an association between exposure to sulfate and the frequency of self-reported diarrhea. Because these studies were not able to establish a dose-response or a level of sulfate in drinking water that would not be expected to cause adverse human health effects, CDC and EPA organized a workshop of scientific experts to present and discuss the most relevant scientific studies conducted on the health effects of sulfate.

Prior to the workshop, the panel members received a document reviewing the relevant scientific literature on the health effects of sulfate. At the workshop, each panelist presented the most current information in his or her field of expertise. The panelists and other workshop participants discussed the information presented in the literature review and presentations, focusing on the four key issues listed below:

Issue 1 Do the studies suggest that a certain contaminant level would not be likely to cause adverse effects (e.g., diarrhea in infants and travelers)?

Issue 2 Does the literature support acclimatization or resistance (what process and time frame does it take)?

Issue 3 Can an infant study be done for dose-response anywhere in the U.S. or Canada?

Issue 4 Is there enough scientific evidence that there are adverse health effects from sulfate in drinking water to warrant regulation? [Congress directed EPA to use the best available science to set drinking water goals and standards.]

Speakers

Opening/Welcome

Michael McGeehin, *Ph.D., M.S.P.H., Chief, Health Studies Branch*

National Center for Environmental Health, Centers for Disease Control and Prevention

Dr. Mike McGeehin, Chief of the Health Studies Branch in the National Center for Environmental Health (NCEH) at the Centers for Disease Control and Prevention (CDC) welcomed the participants, provided a brief background and introduction to the meeting, and introduced Dr. Carl Shy, the facilitator for the workshop. Dr. Shy, from the Department of Epidemiology in the School of Public Health at University of North Carolina at Chapel Hill, gave a brief background on his experience in environmental health. He asked participants to state their names and identify their area of expertise and its relationship to the issue of sulfate in drinking water. Workshop presenters and their areas of expertise regarding sulfate were Dr. Charles Abernathy, sulfate toxicology; Dr. Lorrie Backer, principal investigator for the CDC studies; Dr. Marie Cassidy, interaction between sulfate and the gastrointestinal tract; Dr. David Cole, sulfate biochemistry; Dr. Guillermo Gomez, the effects of sulfate on the gastrointestinal system of piglets; Dr. Marilyn Morris, regulation of sulfates in the body. Other workshop participants were Larry Posey, CDC; Bob Benson, EPA's Denver office; Dale Fronenberger and Bonita Johnson, EPA's Atlanta office; Kimberly Harris and Dorothy Wormbly, EPA's Chicago office; Dr. Fred Hauchman, EPA Office of Research and Development; Irene Dooley and Jennifer Wu, EPA's Office of Ground Water and Drinking Water; Buck Grissom, Agency for Toxic Substances and Disease Registry (ATSDR); Mike Baker, South Dakota Department of Environment and Natural Resources (there are110 public water systems in South Dakota that have high levels of sulfate); Bill Hiatt, representative for a company that manufactures ammonium sulfate; Krishna Parameswaran, involvement with nonferrous mining drinking water supply and site cleanups; Joyce Tsuji, involvement with mining sites; and Stefano Tervi, representative for a mineral water bottling company in Italy. Following the self- introductions, the panelists made their presentations.

EPA's Scientific Work and Regulatory Background

Charles Abernathy, *Ph.D., Toxicologist*

Office of Water, U.S. Environmental Protection Agency

Sulfur has many roles in the human body (e.g., as a part of amino acids). Some sulfates have been employed as medicines in both human and veterinary medicine. For example, the sodium and magnesium salts of sulfate have been employed as laxatives and the zinc salt has been used as an emetic. The water solubility of these sulfate salts probably contributes to the laxative and emetic effects, because the barium and calcium salts are less soluble and generally not effective. The sulfate salts are not usually employed as laxatives or emetics, but $MgSO_4$ (magnesium sulfate, or Epsom salt) is still used as a cathartic.

As mentioned above, sulfate is a natural and necessary constituent in the bodies of humans and other animals. In humans, serum sulfate levels range from 0.25 to 0.38 mmol/L. Sulfate is involved in a number of biochemical activities including the production of chondroitin sulfate and sulfation of exogenous chemicals.

Animal toxicity studies have found acute LD_{50}s of $MgS0_4$ to be 6 g/kg (oral exposure) and 1.2 g/kg (intravenous exposure). There are few data on the chronic effects of exposure to high doses of this substance. Since its potential for carcinogenicity at high doses has not been studied, sulfate would be classified as a Group D carcinogen under EPA's 1996 proposed guidelines (i.e., sulfate would be placed in the "carcinogenicity cannot be determined" group).

There have been a number of studies conducted to determine the toxicity of sulfate in humans. Chien et al. (1968) presented case reports of diarrhea in three infants exposed to water containing sulfate (ranging from 630 to 1,150 mg/L). However, there were other potential causes of the diarrhea in these infants (i.e., consuming infant formula with high osmolarity or the presence of microbial pathogens) that were not thoroughly addressed by the investigators. A survey conducted in North Dakota found a slight increase in the percentage of people (28%) who reported that their drinking water had a laxative effect when the drinking water contained 500 to 1,000 mg/L sulfate compared to the percentage of people (21%) who reported a laxative effect from drinking water that contained <500 mg/L. Sixty-eight percent of people who consumed water with 1,000 to 1,500 mg/L reported a laxative effect. Peterson (1951) analyzed the data from North Dakota and concluded that drinking water containing $\geq$ 750 mg/L sulfate was associated with a self-reported laxative effect whereas drinking water containing $\leq$ 600 mg/L was not. Moore (1952) reanalyzed the data reported by Peterson and found that most people experienced a laxative effect when they drank water that contained >1,000 mg/L sulfate. In 1977, the National Academy of Science (NAS) reported no ill effects in people who ingested water containing $\leq$ 500 mg/L sulfate.

Children, transients, and the elderly are the sensitive sub-populations of interest to EPA because of the potentially high risk of dehydration from diarrhea that might be caused by high levels of sulfate in drinking water.

In the 1970 Community Water Supply Study, the U.S. Public Health Service (USPHS)

measured the sulfate levels in the drinking water sources of nine geographic areas. Sulfate was present in 645 of 658 groundwater supplies and in all 106 surface water supplies sampled. Sulfate levels ranged from <1 to 770 mg/L (with a median of 4.6 mg/L). Only three percent of the water supplies sampled had sulfate levels greater than 250 mg/L.

The Safe Drinking Water Act (SDWA) of 1974 amended the Public Health Service Act and specified that EPA set primary (based on health effects) and secondary (based on aesthetic and organoleptic qualities) drinking water standards.

In a 1975 survey of 625 Interstate Carrier Water Supply Systems, 3.4 percent of the systems had sulfate levels >250 mg/L. The maximum sulfate level found was 978 mg/L. In a survey of Rural Water Supply in the late 1970s, sulfate was found in groundwater at levels from 10 to 1,000 mg/L, (mean = 98 mg/L), and in surface water at levels from 15 to 321 mg/L (mean = 53 mg/L).

Dr. Abernathy presented the following time line of EPA actions regarding sulfate in drinking water:

March 31, 1977	EPA proposed the Secondary Maximum Contaminant Level SMCL of 250 mg/L based on taste (the World Health Organization (WHO) guideline for sulfate is 400 mg/L, based on taste; people's threshold for tasting sulfate ranges from 250-350 mg/L). The Secondary MCL serves as a guideline, not a federally enforceable standard.
July 19, 1979	The final 250 mg/L sulfate Secondary MCL was published and became effective January 19, 1981.
November 13, 1985	EPA proposed a Health Advisory (HA) for sulfate (400 mg/L) to protect infants. As data became available, EPA would reconsider the need for an enforceable standard to protect transients.
1989	A citizen suit was filed against EPA that led to a consent order establishing a deadline for the publication of an MCL for sulfate.
June 25, 1990	EPA proposed an enforceable MCL of 400/500 mg/L for sulfate to protect infants. (the Canadian guideline [not regulation] is 500 mg/L). EPA retained the Secondary MCL of 250 mg/L.

December 20, 1994 EPA proposed an MCL and health effects goal (maximum contaminant level goal [MCLG]) of 500 mg/L, as agreed under the consent order.

The 1996 Amendments to the SDWA established the following deadlines:

February 1999 CDC and EPA must provide a report of jointly conducted studies to establish a reliable dose-response relationship for sulfate, including sensitive sub-populations (i.e., infants and transients).

August 2001 EPA must determine whether or not to regulate sulfate.

February 2005 If the determination is to regulate, EPA must propose the MCL by August 2003 and issue a final rule by February 2005.

In 1994 EPA estimated that approximately 2,000 of the 54,000 public water systems in the U.S. would have sulfate levels higher than 500 mg/L. These systems include 1,241 serving 25-100 people, 493 serving 101-500 people, 194 serving 501 to 3300 people, 27 serving 3301 to 10,000 people, 10 serving 10,000 to 100,000 people, and none serving over 100,000 people. *[Although public water systems serve 249 million people, 95% of the systems serve less than 10,000 people]*.

Discussion

Dr. David Cole asked if pure sulfate solutions have an odor. Dr. Abernathy responded that taste is more evident than odor, but that there is some odor. Dr. Marie Cassidy asked Dr. Abernathy if EPA's mandate is only for sulfate. Dr. Abernathy said that sulfate is one of several substances that EPA is in the process of determining whether or not to regulate. Buck Grissom, ATSDR, asked if pH affected sulfate in water. Dr. Abernathy answered that he was not aware of any effect that pH has on water and sulfate.

Sulfate Biochemistry

David Cole, *MD, Ph.D., F.R.C.P.C., Associate Professor*

Departments of Laboratory Medicine, Medicine and Genetics, University of Toronto

Sulfate (SO_4^{2-}) is a divalent anion. There may be up to one percent sulfate present in gastric fluids. The human body distinguishes sulfate (5.7 angstroms) from phosphate (6 angstroms) and thiosulfate ($S_2O_3^{2-}$) by the distinctive stereospecific molecular configurations of each ion. The body maintains a homeostasis between absorbed inorganic sulfate, sulfate compounds, and renal excretion; membrane transport and regulation contribute to this homeostasis. Inorganic sulfate represents a small fraction of total sulfate in the body, which includes muccopolysaccharides, chondroitin sulfate, glycolipids, steroids, thyroid hormones, peptide hormones (gastrin), oligosaccharides, and xenobiotics (e.g., drugs). As much as 5 to 10 percent of excreted sulfate is excreted as sulfyl esters.

Dr. Cole and his colleagues conducted studies on the shift in homeostasis between pregnant and non-pregnant women. They found that pregnant women reabsorb more sulfate and retain an extracellular pool for placental transfer to the fetus. There are detectable levels of sulfate in amniotic fluid. Toward the third term, the fetus swallows amniotic fluid, which passes through the gastrointestinal tract and is eliminated in urine. The fetus also has higher circulating levels of sulfate than adults do.

A study looking for a gene responsible for diastrophic dysplasia identified the genetic sequence for one of the four known transporters of sulfate. Apparently, a sulfate deficiency arises if this transporter does not function properly. During fetal development, sulfate deficiencies can lead to diastrophic dyplasia (deformed tissues) of the hands and feet, cognitive and behavioral changes, membrane structural deficiencies, early lethality, and malformed cartilage.

Intestinal Physiology of Sulfate

Marie Cassidy, *Ph.D., D.S.C., Associate Professor*

Department of Physiology and Experimental Medicine, George Washington University

Diarrhea affects more people world-wide than any other illness. Diarrhea caused by parasites or infections need not be life-threatening if fluids and electrolytes are replenished in a timely manner because the intestinal lining is replaced every three to four days, thereby washing out parasites or pathogenic microorganisms. At the apical membrane in the intestines, cation and anion transport occurs through the cell wall. The World Health Organization found that introducing solutions of sodium with glucose and amino acids aids in repairing damage to the apical membrane, allowing water to flow through and between the cells and restoring ion transport.

In the small intestine, plasma has the same osmolarity as the lumen. In the large intestine, differences in osmolality between the plasma and the lumen allow water absorption from the lumen into the large intestinal villi.

Normally there is a balance between absorption and secretion in the intestinal villi. The presence of substances that increase the rate at which materials move through the intestine reduces the amount of time available for reabsorption of water and may cause diarrhea. Diarrhea can also result from an increased secretion of water into the intestinal lumen, which may be caused by bacterial toxins *(Vibrio cholerae, Esherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* [seen in AIDS patients], *Bacillus areus, Clostridium perfringens, Kiebsiella, Shigella dysenteriae, and Pnueamoniaea*), bile salts, hormones, or high levels of osmotically active solutes such as sulfate. Congenital diarrhea can be caused by defective sodium chloride absorption.

In addition to the mechanisms discussed above, increased intestinal hydrostatic pressure, luminal distention, high luminal osmolarity, plasma dilution, increased mucosal permeability, increased interstitial hydrostatic pressure, and underlying infections or impairments (e.g., ulcerative colitis) may cause diarrhea.

Osmotic diarrhea results when there is an excess of unabsorbed osmotically active particles (e.g., magnesium hydroxide in antacids) present in the intestinal lumen. For example, magnesium salts, castor oil, and undigested lactose (i.e., in lactose-intolerant individuals) are osmotically active compounds that can produce laxative effects or cause diarrhea. Cholesterol-binding drugs increase the concentration of bile salts in the colon, and may cause diarrhea.

There are antidiarrheal therapies other than sodium, glucose, amino acids, and fluid replacement. Opiates prolong transit time (the amount of time substances are retained in the intestines) and promote more efficient absorption, and alpha-2-adrenergic medications inhibit anion secretion. High concentrations of steroids increase sodium absorption.

In summary, clinical diarrhea is caused by 1) a lack of capacity to absorb fluids or electrolytes, 2) the presence of osmotically active agents in the intestinal lumen, 3) increased propulsion causing decreased contact time, or 4) bacterial toxins that stimulate secretion of

water into the intestinal lumen. The presence of high levels of sulfate in the intestinal lumen would not typically affect normal healthy adults or infants. However, people with pathophysiology, older people taking certain medications (e.g, to treat diabetes, hypertension, high cholesterol), people with underlying intestinal diseases, and infants in tourist areas may be more susceptible to the effects (i.e., diarrhea) of a sudden exposure to high levels of sulfate.

Discussion

Dr. Shy asked whether drugs to inhibit cholesterol interact with sulfate in water to make it more hyper-osmotic. Dr. Cassidy said that she believes they would because anything that will increase the levels of bile salts in the intestines would be likely to cause loose stools. Another concern is that older people may be more susceptible to high sulfate levels if they are taking cholesterol-lowering drugs or if they have underlying health problems.

Effects of High Sulfate Exposures

Marilyn Morris, *Ph.D., Associate Professor*

Department of Pharmaceuticals, State University of New York at Buffalo

Elimination of sulfate occurs through urinary excretion. In the proximal tubule of the kidney, sulfate is reabsorbed across the brush border membrane into the cells and exits via the basolateral membrane. Sulfate and sodium are reabsorbed into renal proximal tubular cells through a part of the membrane sequence known as NaSi-1. The cells comprising the intestinal ileum also contain the genetic sequence for the NaSi-1 transporter. Another transport mechanism, the sodium-independent sulfate anion exchange transport (SAT-1), is present in muscle and brain. Exposure to certain drugs, such as nonsteroidal antinflammatory drug treatments or hormone therapy; changes in dietary levels of sulfate, age, pregnancy; and disease states, such as hypothyroidism, can affect sulfate transport mechanisms.

Bauer (1976) found 85-90% absorption of sulfate at high concentrations; most of the absorption occurred in the ileum. In a recent study, Dr. Morris and her colleagues gave diets containing different amounts of methionine, an amino acid and sulfate-precursor, to rats. A diet containing three times more methionine than the control diet decreased reabsorption of sulfate from the intestine but produced little difference in serum sulfate levels. The researchers concluded that the body can compensate for different levels of sulfate. Compared to the levels of NaSi-1 messenger RNA (mRNA) in control animals, the levels of NaSi-1 mRNA were increased in animals that were fed the low sulfate diets, and decreased in animals that were fed higher levels of methionine in their diets.

In an experiment using neonatal, young, and adult Guinea pigs, the younger animals reabsorbed sulfate and sodium at higher rates than the adult animals did. Peña and Neiberger (1997) reported that young guinea pigs fed diets high in sulfate maintained serum sulfate concentrations within the normal range by increasing urinary excretion of sulfate.

Diastrophic Dysplasia Sulfate Transport (DDST) is an anion exchanger present in the intestine and in many other tissues. The Down Regulated in Adenoma (DRA) gene encodes an intestine-specific membrane sodium-independent sulfate transport protein. This gene is expressed in the normal colon and also in the small intestine of mice and humans. There is a 59% overlap between the genetic sequences for DRA and SAT-1 and a 60% overlap between DRA and DTDST.

At least one series of sulfate anion exchangers is known to be present in the intestine, and there may be others. At this point little is known about the function of these exchangers or about how sulfate absorption is regulated in the intestine.

Cocchett and Levy (1981) reported that, in human research subjects, a single dose of 8g of anhydrous sodium sulfate caused diarrhea. However, 8g of anhydrous sodium, sulfate divided into four 2-gram doses, given at hourly intervals, did not cause diarrhea. In another study (Morris and Levy, 1983), the same millimolar dose of sulfate provided from magnesium sulfate caused adverse effects ranging from upset stomach to diarrhea. Sixty percent of the

sodium sulfate given in divided doses was absorbed, whereas only 35% of the magnesium sulfate was absorbed. These results indicate that the source of the sulfate (e.g., from the magnesium or sodium salt) is important in determining the extent and nature of any potential adverse effects.

The potential adverse effects of high sulfate ingestion include: 1) diarrhea, 2) alterations in sulfation (e.g., metabolism of hormones, catecholamines, and bile acids), and 3) changes in calcium and magnesium metabolism that increase urinary excretion (e.g., increased concentrations of calcium sulfate complexes are found in renal disease patients).

Galinsky and Levy (1981) studied the concentration of acetaminophen in plasma and found that sulfate depletion decreased sulfation, thereby increasing the amount of acetaminophen that remained in plasma. They also found that, in infants, the sulfonation of acetaminophen occurs more efficiently than it does in adults. Freeman and Richards (1979) found that sulfate and creatinine are not removed by dialysis. Patients with acute renal failure tend to have the highest serum sulfate concentrations, but there have been no acute toxic effects noted from sulfate retention in this circumstance.

Discussion

Dr. Cassidy asked about the connection with renal disease. Dr. Morris answered that the connection between the two is related to the failure of reabsorption, that is, decreases in filtration cause serum sulfate concentrations to increase. Dr. Cole said that in a study of premature infants, he found a relationship between increased sulfate loading and the amount of total sulfoester, but no toxic effects. Dr. Shy asked Dr. Morris to clarify her point about how one of the potential adverse effects of high sulfate is a possible alteration in sulfation, and asked if this alteration could influence metabolism. Dr. Morris suggested that altered sulfation could have an impact on metabolism, but stated that this possibility has not been directly examined. However, research has indicated that metabolism may be affected if sulfate concentrations are too low.

[1]Gastrointestinal Effects of Sulfate in Drinking Water: Baby Pig Study

Guillermo Gomez, *Ph.D, M.S., Senior Scientist*

Director, NCSU Piglet Core, Department of Animal Science, North Carolina State University

The study reported herein was conducted at the North Carolina State University (NCSU) Piglet Core through the Center for Gastrointestinal Biology and Disease with a grant from the EPA .[1] This study used artificially-reared neonatal piglets as a model to evaluate the effect of inorganic sulfate on bowel function in human infants. Two experiments were conducted to evaluate the effect of high levels of sulfate on the growth, feed intake, and feces consistency of artificially-reared piglets and to determine the dose at which at least 50% of the pigs developed nonpathogenic diarrhea. The effect of dietary sulfate level on kidney weight and the concentration of sulfate in urine was also assessed.

Newborn piglets were left with their dams for approximately 48 hours and then transferred to an isolated room containing an automated feeding device (Autosow). Piglets were fed a basal diet with no added sulfate and were allowed to adapt to the new environment for a 3- to 4-day period. The Autosow is a machine containing individual cages that regularly aseptically dispenses small volumes of liquid diet according to the weight of each piglet. Piglets were fed liquid diets only and did not have access to drinking water. The diet reservoir was refrigerated; therefore, bacterial growth in the diets was minimal. In each experiment, at the end of the adaptation period (at an average age of 5 days), 40 piglets were weighed and distributed according to body weight, sex, and litter origin into four groups. Ten individually reared piglets per dietary treatment were fed one of four diets containing the following levels of added inorganic sulfate (mg/L of diet), as anhydrous sodium sulfate (USP): 0, 1200, 1600, and 2000 for Experiment 1 (18-day study), and 0, 1800, 2000, and 2200 for Experiment 2 (16-day study). Inorganic sulfate was dissolved in deionized, distilled water before the other dietary ingredients were added. The deionized, distilled water contained <1 mg inorganic sulfate/L; the basal diets of Experiments 1 and 2 contained 277 and 261 mg inorganic sulfate/L, respectively. Details of the experimental protocol have been published elsewhere (Gomez et al., 1995).

The levels of added sulfate did not affect ($p < 0.05$) the growth of the piglets or their feed intake. Whereas 1200 mg added sulfate/L had essentially no effect on feces consistency, levels >1800 mg/L of diet resulted in a persistent, nonpathogenic diarrhea in neonatal piglets. Added sulfate did not affect relative kidney weight ($p < 0.05$). Inorganic sulfate in urine reached maximum concentration in pigs fed diets with 1600 and 1800 mg added sulfate/L in Experiments 1 and 2, respectively ($p < 0.05$), but declined at higher levels. The changes in feces consistency suggest that the level of added dietary inorganic sulfate at which 50% of piglets develop nonpathogenic diarrhea is between 1600 and 1800 mg/L.

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[1] Although the research described in this presentation has been supported by the U.S. EPA, it has not been subjected to agency review and, therefore, does not necessarily reflect the views of the agency.

Discussion

Dr. Morris clarified that the basal amount of sulfate in Dr. Gomez's study was 270 mg/L, that the actual amount of added sulfate was 1,600 mg/L, resulting in a total amount of 1,870 mg/L given to the piglets. Dr. Shy asked if fifty percent of the animals got diarrhea at 1,600-1,800. Dr. Gomez answered that, at 1,600 mg/L 50% of the piglets got diarrhea, but that at 2,000 and 2,200 mg/L, all piglets had diarrhea.

Dr. Shy asked if there was a difference between animals fed 0 mg/L and those fed 1,200 mg/L. Dr. Gomez responded that there was no effect at 1,200 mg/L, so that level was a safe limit for piglets. Dr. Cole pointed out that the definition of "no effect" is subjective. For example, a pediatrician may have a different definition of "no effect" than a mother who observes changes in the number, frequency, and volume of her infant's stools.

Dr. Gomez noted that studying neonatal piglets for three weeks before weaning is comparable to following a baby for six to nine months. While the study measured sulfate in the urine, the equipment did not allow measurement of urine or feces volume. Dr. Cole asked whether the piglets could have shown adaptation at all but the highest sulfate levels. Dr. Gomez said that he did not measure adaptation, but did find that all piglets grew at the same rate, so there was no effect on growth.

Ms. Joyce Tsuji, of Wheeler Environmental Corporation, was surprised that the piglets showed no dehydration or weight loss. Dr. Gomez responded that his group was also surprised by this outcome. He noted that piglets with rotovirus do become dehydrated and eat less.

Health Effects from Exposure to High Levels of Sulfate in Drinking Water

Lorraine Backer, *Ph.D., M.P.H., Epidemiologist*

National Center for Environmental Health, Centers for Disease Control and Prevention

Sulfate is a substance that is occurs naturally in drinking water. Health concerns regarding sulfate in drinking water have been raised because of reports of diarrhea associated with the ingestion of water containing high levels of sulfate. Of particular concern are groups within the general population that may be at greater risk from the laxative effects of sulfate when they experience an abrupt change from drinking water with low sulfate concentrations to drinking water with high sulfate concentrations.

There are very few scientific reports describing the health effects of exposure to sulfate in drinking water, and the concerns regarding sensitive populations are based on case studies and anecdotal reports. One such potentially sensitive population is infants receiving their first bottles containing tap water, either as water alone or as formula mixed with water. Another group of people who could potentially be adversely affected by water with high sulfate concentrations are transient populations (i.e., tourists, hunters, students, and other temporary visitors) and people moving into areas with high sulfate concentrations in the drinking water from areas with low sulfate concentrations in drinking water.

The objective of the CDC/EPA studies on the health effects of exposure to sulfate was to provide additional information regarding whether sensitive populations (infants and transients) may be adversely affected by sudden exposure to drinking water containing high levels of sulfate. Specifically, the researchers involved designed a field investigation of infants exposed to naturally occurring high levels of sulfate in the drinking water provided by public water systems and an experimental trial of exposure in adults.

In collaboration with the State Health Departments of New Mexico, South Dakota, and Texas, we planned a prospective cohort study of infants who would be exposed to tap water used to mix infant formula. We planned to recruit women in their third trimester of pregnancy. Infants were to be enrolled at birth and followed for 4 weeks to determine if there was an association between exposure to drinking water containing varying levels of sulfate and reported cases of diarrhea.

For a woman to be included in our study, she had to be: (1) accessible through a clinic that offers prenatal care, (2) 35 to 36 weeks pregnant (to exclude severely premature infants and to be able to interact with the woman at her next prenatal visit), (3) not planning to breast feed her baby, (4) planning to feed her infant concentrated formula mixed with her home tap water (can be boiled), (5) planning to be at home with her infant for at least one month, (6) living in a home (private house, apartment, mobile home, etc.) that is served by a public water supply and that does not have a water filtration system, and (7) able to read the study instruments in either English or Spanish.

Using historic water quality data for secondary drinking water constituents (including concentrations of sulfate) provided by the states and Geographic Information System (GIS) techniques, we generated maps of the geographic distribution of each water system that

simultaneously identified the level of sulfate in the water and the size of the population each system serves. Based on the GIS maps, the number of expected births in the participating states, the inclusion criteria we have described, and the assumption that 25% of infants are not breast-fed, we planned a six-month recruiting period. We planned to enroll a maximum of 880 infants, 110 each from water systems within the following ranges of sulfate: < 250 mg/L (baseline or comparison group), 251-500 mg/L, 501-700 mg/L ,and a maximum of 550 infants from water systems with sulfate levels greater than 701 mg/L.

We conducted a pilot study of the planned recruitment methods and study instruments in four counties in South Dakota. Local Public Health Nurses, who already had rapport with clinic patients, were hired and trained to recruit study participants and conduct the activities associated with the study. In the 4 counties (served by 3 Community Health Clinics), 72 women were approached about participating in the study during their prenatal visit to the public health clinics. Of these 72 women, 30 were ineligible because they planned to breast-feed their infant, 23 were ineligible because they planned to use water other than tap water to mix infant formula, and 11 were ineligible because they did not meet other eligibility criteria.

Eight women were eligible to participate in the study; three refused, five women agreed to participate, and one woman completed all the study activities. Of the four women who did not complete the study activities, two switched to bottled water as the source of water to mix with infant formula, one chose to use ready-to-feed formula after two weeks of using the powdered formula, and the fourth moved out of the area.

Because we experienced recruiting problems during the pilot study, we developed a self-administered questionnaire (SAQ) to examine tap water use. The questionnaires were developed in both English and Spanish and were provided to all women who came to one of 32 clinics in the previously identified geographic areas of New Mexico, South Dakota, and Texas. The SAQ asked questions about the source of their home tap water, what mothers of infants ≤3 months old were currently feeding their babies, and how currently-pregnant women planned to feed their infants.

Overall, the results from the SAQ indicate that more than half (61%) of pregnant women report planning to breast-feed their infants. In addition, of those who plan to use infant formula mixed with water, most (84%) plan to use water other than tap water. These results are consistent with our experiences during the pilot study and indicate that only a very small percentage of women who live in areas with high levels of sulfate in the tap water provided by public water systems plan to give this water to their infants.

To examine how many of the women who completed the SAQ would have been eligible to participate in our study, we examined the responses of women who received their tap water from public water systems and who did not have filters on their home taps and found that 403 women with infants ≤ 3 months of age and 761 pregnant women met these eligibility criteria. The highest proportions of women who had used or were planning to use tap water to mix infant formula were in the four counties with average sulfate levels ≤ 250 mg/L. Of the 365 pregnant women in areas with sulfate levels > 250 mg/L, 226 (62%) planned to use infant formula. However, only 39 (11%) planned to use infant formula mixed

with their tap water. Of the 183 women with infants ≤3 months old in areas with sulfate levels > 250 mg/L, 151 (83%) used infant formula, but only 35 (19%) reported having used infant formula mixed with their tap water.

The other population potentially sensitive to abrupt exposure to high levels of sulfate in drinking water is transient adults (students, visitors, hunters, etc.). To study the effects on adults of suddenly changing drinking water sources from one that has little or no sulfate to one that is high in sulfate, we conducted an experimental study involving volunteers from Atlanta, Georgia, including CDC employees and employees at the U.S. EPA Region IV office. Volunteers were randomly assigned to one of five sulfate exposure groups (i.e., 0, 250, 500, 800, or 1200 mg/L sulfate from sodium sulfate in bottled drinking water) and were provided with bottled drinking water for six days. The bottled water for days 1, 2, and 6 contained plain water, the bottles for days 3 through 5 contained added sulfate. The unfinished or empty bottles were returned and weighed to determine how much water was consumed each day. Volunteers were blinded to the level of sulfate in their drinking water.

One hundred five study participants were divided among the dose groups as follows: 24 received 0 mg/L sulfate; 10 received 250 mg/L sulfate; 10 received 500 mg/L sulfate; 33 received 800 mg/L sulfate; and 28 received 1200 mg/L sulfate. We analyzed the number of bowel movements recorded each day by study participants. There were no statistically significant differences in the mean number of bowel movements among the groups on days 3, 4, 5, or 6. There were also no statistically significant differences in the mean number of bowel movements reported when comparing days 1 and 2 (the days when there was no sulfate in the water) with days 3, 4, and 5 within each dose group.

The frequencies of diarrhea reported by individuals exposed to varying levels of sulfate in their drinking water are presented in the table. Three different definitions of diarrhea were used: increase in stool volume compared to normal, change in stool consistency to liquid or paste, and increase in volume/change in consistency. Because the effect of sulfate is dependent on both the weight of the participant and the amount of water each consumed (dose/kg of body weight), we used logistic regression to examine the reported frequency of diarrhea (using the three different definitions described above) by sulfate dose ([concentration of sulfate in water x volume of water consumed on days 3, 4, and 5]/body weight) in individuals who reported normal stool volume on days 1 and 2 and who did not have family members who experienced vomiting or diarrhea on days 3, 4, or 5). Sulfate dose was not a statistically significant predictor of diarrhea in any of the models ($p \geq 0.80$ for all models).

Sulfate Dose (mg/L)	n	Osmotic Diarrhea[1] No.[4] (%)	Diarrhea[2] No.[4] (%)	Diarrhea[3] No.[4] (%)
0	24	2/18 (11)	6/16 (38)	5/14 (36)
250	10	0/9	1/7 (14)	1/6 (17)
500	10	1/8 (12)	4/9 (44)	3/8 (38)
800	33	4/26 (15)	7/20 (35)	8/17 (47)
1200	28	5/27 (18)	6/17 (35)	6/17 (35)

[1] Reported as an increase in stool volume on days 3, 4, or 5 and limited to those who reported normal stool volume on days 1 and 2.

[2] Reported as paste-like or liquid stools on days 3, 4, or 5 and limited to those who reported normal stool consistency on days 1 and 2.

[3] Reported as a change in stool bulk or consistency on days 3, 4, or 5 and limited to those who reported normal stools on days 1 and 2.

[4] (Number of people reporting diarrhea on days 3, 4, or 5)/(Number of people who reported normal stools on days 1 and 2 and who did not report a family member ill with vomiting or diarrhea).

To examine the data for a trend toward increased frequency of reports of diarrhea with increasing dose, we included the dose as an ordinal variable in a logistic regression model of osmotic diarrhea. Again, there was no statistically significant increase in reports of diarrhea with increasing dose (one-sided $p = 0.099$).

The over-all purpose of these studies was to examine the association between consumption of tap water containing high levels of sulfate and reports of osmotic diarrhea in susceptible populations (infants and transients, i.e., those acutely exposed). We had to cancel a planned study of infants because we could not identify enough exposed individuals from which to draw a study population. The results of our SAQ examining tap water use indicated that most pregnant women who completed the survey plan to breast-feed their infants. Of those who plan to use formula mixed with water, most do not plan to use tap water to mix the formula. In our experimental trials with adult volunteers, we did not find an association between acute exposure to sodium sulfate in tap water (up to 1200 mg/L) and reports of diarrhea.

The report describing this study, "Health Effects from Exposure to High Levels of Sulfate in Drinking Water," accompanies this workshop summary.

Evaluation of The Association Between Infant Diarrhea and Elevated Levels of Sulfate in Drinking Water: A Case-Control Investigation in South Dakota

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Dr. Emilio Esteban, *et al.* conducted an investigation of diarrhea in infants in South Dakota who ingest water containing various levels of naturally-occurring sulfate. In that state, 110,000 people live in areas (19 counties) with elevated sulfate levels. In these counties, there were 366 births between January and March 1995, and 264 new mothers were interviewed using a telephone questionnaire. The infants were 6.5- to 30-months-old at the time of the interviews. Interviewers asked the mothers report the number and consistency of their infants' bowel movements, whether their infant had diarrhea (defined as 3 or more loose stools in a 24-hour period), and the quantities of water consumed by their infants in the previous seven days. Mothers were also asked to provide a sample of the water they used in the baby's diet. The water samples were analyzed for sulfate levels.

Cases were defined as infants with diarrhea (as reported by the mother) and control subjects were defined as infants who did not develop diarrhea. The mean concentration of sulfate in the water in the homes of cases was 392 mg/L, and in the homes of control subjects was 358 mg/L. Sulfate intake was 31 mg/kg body weight for both groups. Mothers reported diarrhea in nineteen percent of the infants living in households with sulfate levels in tap water > 500 mg/L h, and in 14 percent of infants living in households with sulfate levels < 500 mg/L. This study revealed no association between exposure to sulfate from tap water and subsequent diarrhea.

Discussion

Dr. Cassidy asked if higher sulfate levels match higher calcium or magnesium levels. Dr. Backer said that geographic areas with high sulfate levels in drinking water sources also tend to have high levels of other salts and minerals, but the association is not consistent. Dr. Cassidy asked whether, in the areas of Dr. Backer's study, there is any sort of folklore pertaining to why women are not choosing tap water for formula. Dr. Backer responded that she did not hear any folklore but that the women probably tended not to use tap water for drinking because it smelled and/or tasted bad. Dr. Backer also noted that the areas that have very high sulfate levels tend to be rural and poor. Potential study participants were identified through Women, Infants, and Children (WIC) clinics and it is possible that women reported breast-feeding, even if they had or were planning to bottle-feed their babies, because WIC clinics encourage breast-feeding.

Dr. Morris stated that she thinks researchers might be more successful in getting women to use a certain infant formula if the women were provided, free-of-charge, with a pre-diluted, ready-to-use formula, with known amounts of sulfate. Dr. Abernathy responded to

this proposal by saying that adding sulfate to infant formula poses an ethical problem. The study would only be acceptable to CDC's Institutional Review Board (IRB) if women planning to use tap water to mix infant formula for their newborn infants could be identified in geographic areas with varying levels of sulfate naturally occurring in the tap water. Diane Burkom, from Battelle, added that even trying to influence a mother to use a certain brand of formula that is naturally high in sulfate would be ethically questionable. Also, in the rural areas where the sulfate levels are high, most women were already provided with free infant formula by WIC clinics, leaving little with which to entice the mothers. Dr Cole pointed out that with a large study sample, some diarrhea will inevitably occur that is unrelated to the study, but which might be attributed to the study.

Dr. Cassidy asked Dr. Backer how long the adult study lasted. Dr. Backer responded that it lasted six days, with exposure for three days, in an effort to mimic the effect of transient exposure.

Dr. Cole commented that, in Europe, mineral water (containing up to 250 mg/L sulfate) is considered soothing, indicating that there is a public perception that small amounts of sulfate may be beneficial and that this perception may be supported by the results from the adult study (the lower frequency diarrhea among study participants who consumed water containing 250 mg/L sulfate compared to the group who consumed plain bottled water. However, as Ms. Tsuji mentioned, the 250 mg/L exposure group did have a small sample size ($n = 10$), and the differences in diarrhea frequency between the two groups was not statistically significant.

Dr. Gomez asked if microbial analysis was performed on the bottled water used in the adult study. Dr. Backer indicated that she received a full report of the chemical and microbial analyses done on the lots of water used for the adult study. Dr. Abernathy stated that the American Academy of Pediatrics has guidelines for sulfate levels in drinking water because it has not seen a problem with sulfate ingestion.

Dorothy Wombly, from EPA Region 5, said that most mothers are told not to use tap water for their infants or to boil it before use. Diane Burkom made the point that boiling water for the amount recommended by formula manufacturers (1 minute) would have no effect on the sulfate concentration. Dr. Backer said that people in the study sites were using water from many sources, including kiosks that provided filtered water (from public water systems). Bonita Johnson, from EPA Region 4, asked if the types of food people eat have an effect on diarrhea. Dr. Backer responded that some types of food could have an effect, but that they did not ask about food consumption in the study.

Discussion of Key Issues

Dr. Shy introduced the issues to be discussed by the participants. He stated that the goal of the workshop was not to reach a consensus, and that the discussion should include all points of view. The purpose of the workshop was to discuss the scientific evidence regarding human health effects from exposure to sulfate in drinking water and whether there is sufficient scientific evidence of a dose-response.

Issue 1 ***Do reported studies suggest that a certain sulfate level would not be likely to cause adverse effects (e.g., diarrhea in infants and travelers)?***

Existing data do not identify the level of sulfate in drinking water that would be unlikely to cause adverse human health effects. The panel members noted that the available published literature included reports that piglets in experimental feeding trials and some people experience a laxative effect when consuming diets (piglets) or tap water (humans) containing from 1,000 to 1,200 mg/L of sulfate (as sodium sulfate). However, none of the studies found an increase in diarrhea, dehydration, or weight loss.

Dr. Abernathy clarified that EPA wanted to base any possible sulfate regulation on people who had no specific diseases or underlying conditions. Dr. Cole asked whether this category of people would be separate from the category including infants, elderly, and travelers. Dr. Abernathy said that EPA wants to focus on infants and travelers, and that people who are taking certain medications or have certain diseases would be considered a separate category. Dr. Cassidy stated that it makes a difference whether the exposure is to magnesium or sodium sulfate, and asked if either of these salts had an odor. Dr. Abernathy responded that the regulation, if one were developed, would likely be written for total sulfate level, and would be based on EPA's current interpretation of the statute (SDWA).

Dr. Shy began the discussion by looking at the Heizer *et al.* (1997) study on the intestinal effects of sulfate in drinking water on normal human subjects. He mentioned that, in the dose-response study, the only effect was decreased transit (mouth-to-anus) time. In the single dose study, 1,200 mg/L caused a significant, but mild, increase in mean stool mass. Dr. Shy said that this study is the most important when considering effects on normal adults. Dr. Morris commented that there is no indication from either the literature or the new data presented at the workshop that 500 mg/L is associated with any toxicity. Dr. Shy asked again about the findings regarding 1,200 mg/L in the Heizer *et al.* (1997) study. Dr. Cassidy responded that the level seems to be mildly cathartic but not toxic. Dr. Abernathy said that it was important to note that the study only had 10 subjects, so it would be difficult to make a definitive statement based on such a limited study.

Dr. Cole reiterated Dr. Cassidy's point that, in adults with no other health issues, 500 mg/L seems to be a safe level to ingest in drinking water. Dr. Morris echoed this point by stating that 500 mg/L is shown to be safe in all studies. Dr. Shy asked if the findings in the Chien *et al.* (1968) paper were consistent with the other studies in reporting that exposure to drinking water containing 500 mg/L sulfate had no effect. Dr. Morris noted that in the Chien

et al. (1968) study, the sulfate levels that caused diarrhea in the three infants were 630, 720, and 1,150 mg/L. Dr. Abernathy pointed out that case reports, such as Chien *et al.* (1968), are notoriously difficult to interpret. He observed that there were many uncontrolled variables in that study, such as the osmolarity of the infant formula and the concentrating effect of boiling the water. Dr. Cole added that infant formula in Canada in 1968 was not controlled at all. Even if the formula was dry cows' milk, cows in that area could have ingested high levels of sulfate from their drinking water.

Dr. Shy then asked the panel to consider table of results from the study by Moore (1952), and asked, if they could say there was no laxative effect at different levels of sulfate. Dr. Cole said that the Moore (1952) study was a bivariate analysis, and that it was possible that, if one conducted a multivariate analysis of the data (considering, for example, the relationship of iron in some of the waters), there might be different results. Dr. Abernathy said that he was not able to get the original data from that study to do a multivariate analysis. In response to Dr. Cole's mention of iron as a possible variable in a multivariate analysis, Dr. Cassidy added that iron causes a constipation effect, not a laxative effect. Dr. Gomez pointed out that the Moore (1952) paper does not look at how persistent the effects were. Dr. Abernathy also added that it was a questionnaire with subjective answers to the question about diarrhea.

Dr. Shy cautioned participants to remember that they were trying to determine the level of sulfate at which there is no human health effect. Irene Dooley reiterated that the results from the studies conducted by CDC and EPA did not find a dose-response association between exposure to sulfate in drinking water and diarrhea; therefore, the literature and this workshop will be key sources of information when the agency makes a regulatory determination. Adding to this clarification, Dr. Abernathy said that the workshop panelists do not have to agree on a definitive value. The EPA would like to know whether anyone would be comfortable saying that "at X mg/L of sulfate in drinking water a healthy human is unlikely to have an adverse health effect, but the likelihood of experiencing an adverse health effect may increase with increasing sulfate levels."

Dr. Backer asked if the panelists, in defining the health outcome, are looking for a laxative effect or diarrhea specifically. She pointed out that the distinction is not made clear in the different studies. Dr. Cassidy clarified that a laxative effect can be beneficial, but constant diarrhea can cause problems. Dr. Cassidy stated that clinical diarrhea must be chronic to be considered a problem for an individual. Dr. Abernathy said a doctor told him that gastrointestinal distress lasting a week is not a problem for a healthy tourist. Dr. Cole said that diarrhea can be defined as 1) what a mother perceives as diarrhea, or 2) a situation that actually warrants an emergency room visit for intervention because of dehydration, based on stool volume and frequency. He noted that since the American Pediatric Association issues nothing about sulfate, it doesn't perceive a correlation between sulfate and diarrhea.

Dr. Shy pointed out that Moore (1952) looked at a "laxative effect," which is not necessarily an adverse human health effect. Dr. Morris suggested that we can take 0-200 mg/L as a baseline. At 500-1,000 mg/L there is only a 10 percent increase in laxative effect, and at 1,000 mg/L 62% of respondents report experiencing a laxative effect.

Dr. Shy brought the discussion back to the Heizer *et al.* (1997) study. In this study, six people drank plain water (containing no added sulfate) for six days, followed by six more days in which they drank water containing 1,200 mg/L added sulfate. Study participants did not report having diarrhea (no increase in stool frequency or consistency), but did report an increase in stool bulk. This study was controlled (although small) and did not show adverse health effects in adults from exposure to sulfate in drinking water. The second study reported by Heizer *et al.* (1997) involved a gradual increase in sulfate level. There were no reported health effects from this exposure. Dr. Morris noted that the Heizer *et al.* (1997) study used sodium sulfate. Dr. Gomez stated that, in his study of baby pigs exposed to 1,200 mg/L sulfate (as sodium sulfate), the pigs did not get diarrhea.

Dr. Shy then raised the question of special populations, such as neonates. He reiterated that the Esteban *et al.* (1997) study included infants (6.5 to 30 months of age), but found no association between the level of sulfate exposure and diarrhea reported by the mothers. Dr. Cassidy pointed out that the Chien *et al.* (1968) study involved only three infants. Dr. Shy repeated that we do not know the total amount of sulfate (including formula and tap water) that the infants received in the Chien *et al.* (1968) report. They received at least 630 mg/L, but the amount could have been higher. Dr. Cassidy said that Chien *et al.* (1968) proposed 400 mg/L as a tentative acceptable level for infants. She added that there is no evidence in the literature that sulfate causes problems for the elderly.

Bob Benson, from EPA Region 8, referring to Dr. Cole's comment that water with sulfate levels of $\geq$ 1,000 mg/L are hyper-osmolar, asked at what point the osmotic pressure in the lumen would equal the osmotic pressure in the intercellular fluid. Dr. Cole responded that, for sodium sulfate, the concentration would be close to 40,000 μosmoles of sulfate. The study by Gomez *et al.* (1995) shows that even though sulfate anions are not enough to draw intracellular fluid into the lumen, sulfate interaction with the cellular structure affects the transfer of water. Also, there is some biological evidence to suggest that sulfate does interact to change cellular physiology in the gut. However, the Gomez *et al.* (1995) study showed that the diarrhea observed in the piglets is not purely an osmotic diarrhea because that would be expected produce weight loss and dehydration, and the piglets did not experience either.

Dr. Cassidy reported that there is also a physiological mechanism that balances the effects of changes in osmolarity and maintains ion and water transport across the lumen. Even with hyper-osmolar diarrhea, the body eventually will adjust the osmolarity of the lumen to balance water absorption and loss.

Issue #2 ***Does the literature support acclimatization or adaptation (what process and time frame does it take)?***

Based on biologic plausibility and anecdotal reports, evidence indicates that people acclimate to the presence of sulfate in drinking water. In addition, serum sulfate levels are high (compared to adults) in human fetuses and neonates (to support rapid growth and development). However, data describing acclimation and the changes in sulfate metabolism during growth and development are limited.

Dr. Cassidy responded that there is very little information on acclimatization, but, based on pathogenic responses, evidence indicates that sulfate acclimatization would probably occur within 3-4 cell cycles, over the course of one to two weeks. Dr. Cole indicated that his opinion, based on kidney changes, Gomez's study, clinical results, and anecdotal evidences, is that acclimation is a theoretically possible biologic process. Dr Cole suggested, however, that the evidence that acclimation occurs is not fully convincing. Dr. Gomez said that in his relatively long, 18-day study, the piglets did seem to acclimate to sulfate.

Dr. Shy asked the participants to consider the issue of travelers versus residents and Dr. Morris asked if EPA would consider setting levels for all people living in an area or just for infants starting on formula and travelers? Dr. Abernathy mentioned that EPA has considered, in the previous proposal, posting signs for travelers. He added that providing bottled water for infants in certain areas is also an option.

Ms. Tsuji asked if neonates acclimate faster because they are growing. She also asked if the data presented by Dr. Cole regarding high sulfate levels in amniotic fluid suggested that infants suffer fewer adverse health effects from exposure to high levels of sulfate because they acclimate more quickly. Dr. Cole responded that both intra-cellular sulfate and intervascular sulfate are elevated before birth and during some period after birth to support growth and development. But the infant gastrointestinal tract is somewhat more permeable to salts and is more sensitive than that of an adult. If powdered milk (which has high osmolarity) is pushing the infant gastrointestinal tract to its limit, high levels of sulfate from another source (such as tap water) could cause diarrhea. Dr. Cassidy added that the configuration and shape of the infant's intestinal cells depend on the diet. Dr. Morris stated that sulfate transport mechanisms develop over time, and that the process has not been studied. Bat (1969) found that, in adult rats, transport and absorption occurred in the ileum. Neonatal rats had a different distribution of sulfate in tissues, suggesting changes in the mechanisms of sulfate absorption during different stages of development.

Bill Hiatt, from BASF Corporation, suggested that a developmental effect would justify a higher level of concern for establishing a primary drinking water standard than would a transitory effect among travelers. Dr. Cole noted that people may be likely to protect their infants by using bottled water.

Issue #3 ***Can an infant study be done for dose-response anywhere in the U.S. or Canada?***

The difficulty in locating a population of women feeding their infants formula mixed with unfiltered tap water containing high levels of sulfate hinders the completion of an infant study of the dose-response to sulfate exposure. A study using neonatal pigs could assess a dose response for both magnesium and sodium sulfates.

Dr. Backer began by stating her opinion, based on recruitment efforts for the study she attempted to conduct, that it is not possible to do a population-based study in the United States that includes infants naturally exposed to varying levels of sulfate from tap water provided by public water systems. Dr. Cassidy said that such a study could be done only as an

animal study, and that piglets are the best model to use. She added that such a study could include intestinal biopsies to establish the mechanism by which sulfate exerts its effects. She also suggested looking at other parameters as well, such as renal function.

Irene Dooley said that EPA traditionally uses a safety factor of 10 for transfer of animal to human results, which, for the Gomez *et al.* (1995) study, would suggest limiting levels of sulfate to 160-220 mg/L. Dr. Cole responded that, while there perhaps should be a factor, in this case he does not think a factor of 10 makes sense because there is no biotransformation (*e.g.* activation) of the compound. Mr. Benson asked panelists if they agree that a safety factor of 10 was not needed when extrapolating from piglets to humans. Dr. Cassidy said that researchers do not use pigs often because they are very expensive, but they are much better models for human intestinal physiology than other animals such as rodents (i.e., studies have shown that the tissue in the gut of piglets and infant humans is very similar).

Dr. Abernathy explained that FDA, in 1954, derived a safety factor of 100 for "no-observed effect levels" (NOEL) of animal studies. Since that time, the safety factor has been split into two 10-fold multipliers (a 10-fold safety factor when extrapolating from normal to sensitive humans and a 10-fold safety factor when extrapolating from animals to humans). Empirical data compiled by Dourson and Stara (1983) has shown that the variation among various factors, e.g., subchronic to chronic effects, could often be accounted for by using a 3-fold factor, indicating that the usual 10-fold factors are sufficient. The World Health Organization referred to these factors an acceptable daily intake (ADI) and safety factor (SF), but EPA now uses the terms Reference Dose (RfD) and Uncertainty Factors (UF). However, depending on the completeness of the data base, the 10-fold UF does not have to be employed. For example, the data base on nitrate/nitrite and fluoride contained a lot of data on human exposures, and EPA used an UF of one.

Dr. Cole stated that results using the piglet model of human intestinal physiology would require a safety factor less of than 10. He mentioned that Stephanie Atkinson studied the tolerance of phosphate in infant formula by neonates, particularly low-birth weight and premature infants. Data on the effects in neonatal piglets was directly comparable to that on the effects in human infants (i.e., no safety factors were applied). Dr. Cole suggested a safety factor between 1.5 and 2 for neonatal piglets and human infants.

Dr. Gomez added that an important component of this kind of research is that work with baby pigs is done in departments of animal veterinary sciences, but should be done in connection with medical schools (especially by pediatricians).

Dr. Shy summarized the panelists' discussion, including the need for a dose-response study using an animal model and the determination of an appropriate safety factor for extrapolation of results from animals to humans. Dr. Cassidy added that it would be important to also look at magnesium sulfate, as well as sodium sulfate.

Dr. Shy said that we can assume that other countries have areas where the sulfate levels in drinking water are high, but asked if an infant study be ethically acceptable. Dr. Cassidy repeated Dr. Cole's observation that said it would be unlikely that researchers could identify an exposed infant population, partly because if infants get diarrhea, mothers will find

an alternate source of water. Dr. Shy wondered whether it would be possible to identify exposed infants if a study were to start with new mothers. Dr. Cassidy brought up the possibility of doing a pediatric survey in Europe where sulfate levels are high. Dr. Cole cautioned that those surveys cannot always eliminate the effects of other constituents of drinking water. He suggested that such a survey could be done in the developing world, but that doing so may be logistically difficult. He added that women everywhere use the cleanest water for their infants. Diane Burkom, from Battelle, said that in considering other possible sources of the diarrhea, the researchers limited their study to public water supplies because private wells have a higher risk for bacterial contamination than public water supplies do. Dr. Cassidy added that pathologic bacterial diarrhea would be an issue in the developing world.

Dr. Shy asked about conducting a randomized trial in a place that had a natural sulfate level of 1,000 mg/L and no alternative water sources. Study participants could be provided with water containing either 0 or 500 mg/L added sulfate, and the health outcome would be diarrhea. He asked panelists whether such a trial would be ethically acceptable, pointing out that if the trial is conducted at a site which has a normal sulfate level of 1,000 mg/L, and no other water supply choices, the study would provide study subjects with water that contained less sulfate than they normally would be exposed to. Dr. Gomez said that Peru uses rainwater, which is easy to collect, as a source of drinking water and that hygiene and viruses are more difficult to control in a developing country. Dr. Cole said a study would be theoretically possible, but that an Institutional Review Board (IRB) would not sanction the protocol, since the researchers would, after determining that the high levels of sulfate caused illness, possibly leave the community and not provide a permanent source of improved water. Dr. Cassidy added that she did not know of a population in which diarrhea is not bacteriologic.

Dr. Morris said that maybe one could do such a study in the U.S. or Canada, but that there is a need for more animal studies. Dr. Shy said a randomized trial would take care of the uncertainty of the baseline diarrhea level, and Dr. Backer replied that she could not locate 1000 babies in the U.S. to do such a study. Dr. Gomez asked if it is possible to lower sulfate levels in areas where it is high. Irene Dooley responded that treatments such as reverse osmosis and ion exchange are possible, but it could be costly to require that all public water systems meet a level of 500 mg/L. Michael Baker, from the South Dakota Department of Environment and Natural Resources, Drinking Water Program, said that South Dakota did an analysis of the water systems that exceed 500 mg/L and estimated that it would cost $60 million to lower the sulfate levels the 110 systems in the state to 500 mg/L. The average household cost for public water in South Dakota is approximately $9 per month for water, but would increase to approximately $28 per month to compensate for the cost of treatment to remove sulfate (reverse osmosis and ion exchange). South Dakota systems would likely chose to convert to using surface water sources for drinking water rather than to remove sulfate from ground water. Removing sulfate from drinking water would also be a financial burden on the water treatment facilities. All but 27 systems with $\geq$ 500 mg/L sulfate are in low-income areas. The rest serve cloistered religious communities. Dr. Cassidy asked if there are public health reports of increased physician visits in areas with high sulfate? Mr. Baker said that his department did a non-scientific polling of 27 pediatricians and several family

practitioners, and none reported ever treating diarrhea caused by exposure to sulfate.

Dr. Abernathy stated that the 1977 National Academy of Sciences (NAS) report concluded that there are no adverse human health effects associated with exposure to 500 mg/L sulfate or less, but EPA would need to study the data used to support that conclusion.

Dr. Cole asked Mr. Baker if there is a relationship between sulfate content and the population's use of water for cooking, drinking, coffee, etc. Mr. Baker that sulfates come from wells that are dug into the geologic formation called the Dakota Formation, and there has always been an objection to the taste of this water; it makes terrible coffee. The levels of dissolved solids are also high; however, before 1965, people used the water because they had no choice. Using Rural Water Assistance grants, 39 systems switched to surface water for aesthetic reasons. Now people can choose to purchase bottled water or install reverse osmosis filtration systems in their homes. When Mr. Baker looked for health effects from drinking water that contained high levels of sulfate, he found only one physician's assistant who treated three youths from a combine crew who reported diarrhea after drinking community water that contained 1,200 mg/L sulfate. However, these individuals were drinking very large quantities of water (5 to 10 liters per day per person). Dr. Backer added that in their infants sulfate study areas, people also used filters and bottled water for aesthetic purposes.

Dr. Shy repeated that Dr. Abernathy's statement that by 2001 EPA must decide whether or not to regulate sulfate, and asked whether EPA can regulate substances for reasons other than health risk.. Dr. Abernathy said that EPA regulations can be based only on the need to reduce the frequency of adverse health effects, but that States can issue regulations for aesthetic reasons, such as taste.

Dr. Shy asked if there exists adequate scientific evidence that there are adverse health effects associated with high levels of sulfate in drinking water. Dr. Abernathy asked whether the workshop might consider making this question Issue 4. Dr. Backer wanted to know what EPA's non-regulatory options are. Irene Dooley responded that if EPA decides not to regulate the levels of sulfate in drinking water, EPA could keep the current secondary guideline of 250 mg/L, which is based on taste and odor. EPA can also put out health advisories or consumer advisories in localized areas.

Issue #4 ***Is there adequate scientific evidence that there are adverse health effects from sulfate in drinking water to support regulation?***

While there is not enough scientific evidence on which to base a regulation, a health advisory in places that have sulfate levels of 500 mg/L or higher would acknowledge the needs of sensitive subpopulations.

Dr. Shy briefly summarized the studies by Moore (1952), Heizer *et al.* (1997), Esteban *et al.* (1997), and Gomez *et al.* (1995). The Moore (1952) study found a laxative effect in water with high levels of sulfate. The Heizer *et al.* (1997) study found that adults who ingested 1,200 mg/L sulfate had no diarrhea but reported increased stool bulk. Esteban *et al.* (1997) found no increases in diarrhea in infants who ingested water containing up to 1350 mg/L sulfate, but the study had a small sample size and thus limited power to detect an association. Gomez *et al.* (1995), found no effect in the frequency of diarrhea in piglets fed a diet that contained 1,200 mg/L sulfate. Fifty percent of the piglets given 1,600-1,800 mg/L sulfate had; however, the diarrhea did not affect weight of the piglets.

Dr. Cassidy wanted to know the range of sulfate levels currently found in tap water. Dr. Abernathy said that surveys indicated about 3% of the tap water in the U.S. exceeds 250 mg/L, and levels up to 770 to 1,000 mg/L have been measured. For the 1994 proposal to regulate sulfate, EPA estimated about 1965 public water supplies would exceed 500 mg/L. Mr. Baker said that community systems in South Dakota may have sulfate levels as high as 1,350 mg/L, and some private wells are higher (up to 2,000 mg/L sulfate). Dr. Morris stated that healthy adults would have no problem with 1500 mg/L. However, she cautioned that mothers of infants, the elderly, and people with certain health problems may need to be cautious when using for drinking water containing high levels of sulfate.

Dr. Abernathy informed the panelists that even if EPA decides that scientific evidence cannot support issuing a federal regulation, states may still choose to regulate the amount of sulfate in drinking water. Kim Harris, from EPA Region 5, told participants that if EPA decides not to regulate sulfate, the potential health risks for susceptible populations will still be addressed (e.g., with health advisories similar to those created for *cryptosporidium*).

Dr. Cassidy asked if there are surveillance or reporting data describing sulfate levels in public water systems. Irene Dooley answered that there is a requirement to report sulfate levels based on the unregulated contaminant monitoring requirements of 1992. EPA is in the process of analyzing this data from the states. Dr. Cassidy asked if this data contains reports of diarrhea or other adverse health effects. Dr. Backer responded that CDC and EPA are developing a study to establish a national baseline for gastrointestinal illness. One challenge associated with collecting this type of data is that when people have diarrhea, they usually go to the drug store, not a doctor. Dr. Backer pointed out that monitoring the purchases of over-the-counter medications in geographically defined areas can be an alternative approach for evaluating localized gastrointestinal distress.

Dr. Shy directly asked the panelists if there is an answer to Issue 4. Dr. Cole answered that there is nothing in the literature regarding effects in healthy adults from exposure to high

levels of sulfate in drinking water, but that he believes that a health advisory would be in the best interest for infants. He also said that an advisory for elderly people and for travelers would be appropriate. Dr. Cassidy agreed with Dr. Cole that there is not enough scientific evidence to indicate that exposure to high levels of sulfate causes adverse human health effects.

Dr. Abernathy stated that EPA needs to specify a safe level, even in a health advisory. He suggested that EPA could, for example, set a health advisory at 500 mg/L.

Dr. Morris answered that there is not enough evidence to support a health-based regulation for sulfate levels for healthy adults. The populations of concern are infants, the elderly, and people with health problems. Dr. Morris said that, in her opinion, information from the available literature is that, 500 mg/L may be protective, but additional studies need to be done to identify the appropriate concentration.

Dr. Gomez noted that special attention should be given to states that have a potential problem. Ms. Tsuji added that it appears that while 3% of 200 million (6 million), people are exposed, it is hard to find them, and we cannot be sure what else is in their water, so it may be better to manage through pediatricians, the health department, and WIC clinics, and on an individual level instead of trying to regulate at a national level. She noted that sulfate does not cause irreversible damage, and that regulating other water contaminants is more urgent. Mr. Baker gave his opinion that he is not in favor of regulating sulfate at this point, because people are resolving the problem.

Dr. Shy summarized by saying no one study can provide a dose-response relationship for sulfate, and that other studies are necessary. The existing literature supports issuing health advisories, especially for infants, that sulfate levels > 500 mg/L may have negative health effects. Dr. Cole reiterated his belief that it would not be possible to conduct an infant study in the U.S. or Canada and that he does not believe the literature indicates acclimitization. Krishna Parameswaran stated that his company has three mining sites in the west in areas with sulfates in the drinking water, and the workers there do not experience diarrhea.

Literature Cited

Bauer JH. Oral administration of radioactive sulfate to measure extracellular fluid space in man. J Appl Physiol. 1976;40(No.4):648-650.

Chien L, Robertson H, Gerrard JW. Infantile gastroenteritis due to water with high sulfate content. Can Med Assoc J. 1968; 99: 102-104.

Cocchetto DM, Levy G. Absorption of orally administered sodium sulfate in humans. J Pharm Sci. 1981;7(No. 3):331-333.

Dourson ML, Stara JF. Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol. 1983;3:224-238.

Esteban, E, Rubin CH, McGeehin MA, Flanders WD, Baker MJ, and Sinks TH. Evaluation of infant diarrhea associated with elevated levels of sulfate in drinking water: a case-control investigation in South Dakota. Int J Occup Med Environ Health. 1997; 3(3): 171-176.

Freeman RM, Richards CJ. Studies on sulfate in end-stage renal disease. Kidney Int 1979;15(2):167-75.

Galinsky RE, Levy G. Dose- and time-dependent elimination of acetaminophen in rats: pharmacokinetic implications of cosubstrate depletion. J Pharmacol Exp Ther 1981;219(No. 1):14-20.

Gomez GG, Sandler RS, Seal, E Jr. High levels of inorganic sulfate cause diarrhea in neonatal piglets. J Nutr. 1995;125: 2325-2332.

Heizer WD, Sandler RS, Seal E Jr, Murray SC, Busby MG, Schliebe BG, and Pusek SN. Intestinal effects of sulfate in drinking water on normal human subjects. Dig Dis Sci 42(5): 1055-1061.

Moore EW. Physiological effects of the consumption of saline drinking water. A progress report to the 16th meeting of the Subcommittee on Sanitary Engineering and Environment. Appendix B. January 1952. Washington, DC: National Academy of Sciences. 1952.

Morris ME, Levy G. Absorption of sulfate from orally administered magnesium sulfate in man. J Toxicol Clin Toxicol. 1983;20(2): 107-114.

Peña DR, Neiberger RE. Renal brush border sodium-sulfate cotransport in guinea pig: effect of age and diet. Pediatr Nephrol 1997;11(No. 6):724-727

Peterson NL. Sulfates in drinking water. Official Bulletin: North Dakota Water and Sewage Works Conference 1951;18(10&11): 6-11.

Appendix A: Workshop Agenda

The Health Effects from Exposure to Sulfate
in Drinking Water Workshop

Agenda

8:30-8:50 Registration

8:50-9:00 Welcome & Purpose of Meeting
Michael A. McGeehin, Ph.D., M.S.P.H., NCEH, CDC

9:00-9:10 Introduction of Workshop Facilitator
Carl Shy, MD, University of North Carolina at Chapel Hill

9:10-9:25 EPA's Scientific Work, Safe Drinking Water Statute & Regulatory Background
Charles Abernathy, Ph.D., Office of Science and Technology, EPA

9:25-9:40 Sulfate Biochemistry
David Cole, MD, University of Toronto

9:40-9:55 Intestinal Physiology
Marie Cassidy, Ph.D., D.S.C., George Washington University

9:59:55-10:10 Effects of High Sulfate Exposures
Marilyn Morris, Ph.D., School of Pharmacy, SUNY-Buffalo, NY.

10:10-10:25 BREAK

10:25-10:55 Health Effects from Exposure to High Levels of Sulfate in Drinking Water

Lorraine Backer, Ph.D., M.P.H., NCEH,

10:55-11:10 Animal Studies
Guillermo Gomez, Ph.D., North Carolina State University

11:10-11:15 Presentation of Issues
Carl Shy, M.D., M.S.P.H., University of North Carolina

11:15-12:00 Facilitated Panel Discussion of Issue 1
Carl Shy, M.D., M.S.P.H., University of North Carolina

12:00-1:00 LUNCH

1:00-1:45 Facilitated Panel Discussion of Issue 2
Carl Shy, M.D., M.S.P.H., University of North Carolina

1:45-3:00 Facilitated Panel Discussion of Issue 3
Carl Shy, M.D., M.S.P.H., University of North Carolina

3:00-3:15 BREAK

3:15-3:45 Facilitated Panel Discussion of Issue 4
Carl Shy, M.D., M.S.P.H., University of North Carolina

3:45-4:15 Facilitated Discussion: comments from the public
Carl Shy, M.D., M.S.P.H., University of North Carolina

4:15-4:30 Next Steps and Adjourn
Carl Shy, M.D., M.S.P.H., University of North Carolina

Appendix B: List of Participants

Health Effects from Exposure to High Levels of Sulfate in Drinking Water Workshop

September 28, 1998

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