Brief profiles on systemic toxicological effects of common counter-ions in metal substances:

6. Sulfate

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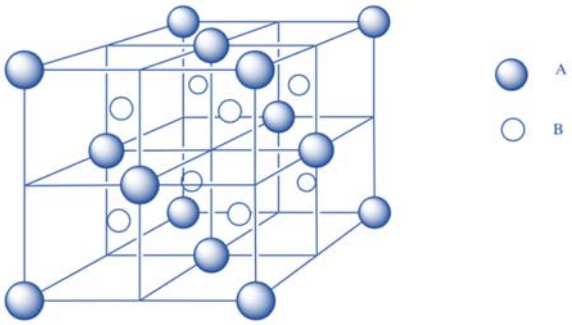

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Sulfate: Brief profile on systemic toxicological effects

For information on background, scope and use of this document, see accompanying cover-note!

1. Identification

Name: sulfate (anion)
Chemical formula: SO_4^{2-}
Molecular mass: 96.06 g/mol

2. Introductory remarks

Ions such as sulfate (SO_4^{2-}) are not defined as a substance under REACH since they are always associated with a counterions to maintain electrical neutrality (formation of "salts"). The toxicology of such salts is always a combination of both ions, so that toxicological information is – in most cases - not available for the ion on its own. Sulfate is a common anion in salts e.g. of alkaline or alkaline-earth metals. The aim of this summary on the systemic toxicity of sulfate is to assist the assessor of health hazards of sulfate containing substances, in determining whether the sulfate moiety contributes to the overall toxicity of the substance. This document does not discuss primary literature or studies in detail. Instead, reference is made to most recently published authoritative reviews (e.g. European Food Safety Authority or WHO).

3. Natural occurrence, physiological function and dietary intake

Sulfate is a naturally occurring anion which is abundantly present in the environment (e.g. as part of minerals, in water and in biota) and also plays an important role for the ionic balance in body fluids in the human body. Sulfates are also found in many frequently used personal care products (e.g. shampoo, facial cleansers, toothpaste, etc.) that are considered as safe. EFSA has concluded that a daily intake of sulphate ions up to 6 g/day (100 mg sulphate ion/kg bw/day) does not give rise to concern (EFSA, 2008).

4. Toxicokinetics

Sulfate is a normal constituent of blood, is a normal metabolite of sulfur-containing amino acids, and excess sulfate is excreted in the urine. Daily sulfate excretion is reported to be 0.20 to 0.25 mmol/kg bw/day and higher in children (Health Canada 1987, updated 1994).
In humans, the absorption of small amounts of sulfate from the gut occurs rapidly and almost completely. In a study with 8 volunteers, small amounts (60-80 µCi) of radioactive sulfate-35 (^{35}S) were administered orally or intravenously. Plasma equilibrium was reached within 60 to 105 and 60 to 90 minutes respectively, and in both cases 80% or more of the administered amount of radioactivity was recovered in the urine within 24 hours (Bauer et al, 1976).
After absorption, free sulfate ions rapidly distribute over the extracellular space, the apparent volume of distribution being ~ 20% of the body volume. The serum concentration of sulfate in humans ranges between 1.4 and 4.8 mg/100 mL, with a mean of about 3.1 mg/100 mL. Excretion is mainly in urine. The renal clearance is approximately one third of the glomerular filtration rate, indication tubular re-absorption. However, the total free sulfate excretion rate is not dependent on urine flow rate. Organically bound sulfate may follow different excretion patterns. (Cocchetto and Levi, 1981).
About 800 mg of elemental sulfur are eliminated daily through the urine of humans, compared with 140 mg in the faeces. (ICRP, 1984) Some 85% of urinary sulfur is present as inorganic sulfates and a further 10% as organic sulfates, whereas the remainder is excreted as conjugated alkyl sulfates (Diem, 1972).
Similar data are available from experimental animals: In a study on male Wistar rats using ^{35}S labelled Na_2SO_4, rapid and almost complete absorption occurred. When the radioactively labelled material was

added to a large amount of unlabelled sodium sulfate and subsequently orally administered, the plasma peak occurred at the same time, but the amount of radioactivity decreased as the dose of unlabelled sulfate increased. This indicates that there is a saturation of the absorption mechanism (Krijgsheld, 1979).

5. Toxicological effects

Sulfate anions are abundantly present in the human body in which they play an important role for the ionic balance in body fluids. Sodium and magnesium sulfate are also used clinically as a laxative. In clinical trials in humans using 2-4 single oral doses of up to 4500 mg sodium sulphate decahydrate per person (9000 – 18000 mg per person), only occasional loose stools were reported. These doses correspond to 2700 - 5400 mg sulphate ion per person. High bolus dose intake of sulphate ion may lead to gastrointestinal discomfort in some individuals. No further adverse effects were reported (JECFA 2000, 2002). This position was adopted by the European Food Safety Authority (EFSA 2004) without alteration. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concludes that the few available studies in experimental animals do not raise any concern about the toxicity of the sulfate ion in sodium sulfate. Standard toxicological data cannot be generated for the sulfate ion on its own, since it is always present in a substance. The information in the subchapters below is therefore often based on the substance sodium sulfate, a soluble sulfate salt.

5.1. Acute toxicity

The acute toxicity (LD_{50}) of sodium sulfate has not been reliably established but is probably far in excess of 5,000 mg/kg. In an inhalation study, no adverse effects were found at an aerosol exposure of 10 mg/m^3. Also, human data indicate a very low acute toxicity of sodium sulfate. Human clinical experience indicates that very high oral doses of sodium sulfate up to 300 mg/kg$_{bw}$ (i.e. up to 20 grams for an adult) are well tolerated, except for causing severe diarrhoea. WHO/FAO did not set an ADI for sodium sulfate. There is no data on acute dermal toxicity, but this is probably of no concern because of total ionisation in solution (SIDS Initial Assessment Report, sodium sulfate 2005).

The laxative effect of oral ingestion is well known and is therefore used medicinally. High dosages given in medical practice with the purpose of inducing diarrhoea were usually accompanied by severe abdominal cramps. Apart from that, no side effects are mentioned in the medical literature.

5.2. Sensitisation

Sulfate is unlikely to cause allergy, since the body contains large amounts of sulfate (~0.33 mmol/L in serum and about 50 times higher concentration intracellularly). Based on the above, it may be concluded that the sulfate anion is not an allergen in humans. Despite the absence of formal study results, it can be concluded based on the natural intra- and extracellular occurrence of the substance, that sensitisation to sulfate is highly unlikely.

5.3. Repeated dose toxicity

No suitable dermal and inhalation repeated-dose toxicity studies are available. Valid oral repeated dose toxicity studies with sodium sulfate in hens and pigs with 21, 28 and 35 days study duration are available. Toxicity was confined to changes in bodyweight, water and feed intake and diarrhoea. These changes occurred only at very high doses of sodium sulfate. In ruminants, high concentrations of sulfate in food may result in the formation of toxic amounts of sulfites by bacterial reduction the rumen, leading to poly-encephalomalacia. The available data do not allow the derivation of a NOAEL. Based on available consumer data, a daily dose of around 25 mg/kg$_{bw}$/d is well tolerated by humans (SIDS Initial Assessment Report, sodium sulfate 2005).

5.4. Mutagenicity/genotoxicity

Based on the natural intra- and extracellular occurrence of the substance, it can be concluded that sodium sulfate is highly unlikely to be mutagenic. There are no data on in vitro and in vivo genotoxicity, apart from a negative Ames test (SIDS Initial Assessment Report, sodium sulfate 2005).

5.5. Reproductive toxicity

The limited available data give no indication that sodium sulfate is toxic for reproduction. With regard to the natural occurrence of the substance in the body, developmental toxicity is very unlikely (SIDS, 2005).

5.6. Carcinogenicity

There is no valid oral carcinogenicity study. Limited data from experimental studies support the notion that a substance that is abundantly present in and essential to the body is unlikely to be carcinogenic (SIDS,2005).

6. Discussion and conclusion

EFSA has reviewed available data that would allow to derive dietary reference values for sulfate from different sources. Based on the available information, the Panel concluded that a daily intake of sulfate ion up to 6 g/day (100 mg sulfate ion/kg_{bw}/day) for a 60 kg person does not give rise to concern (EFSA, 2008 and 2010).

Sulfate "in a nutshell":

Key / leading adverse systemic effect on human health:	gastrointestinal discomfort/diarrhoea (deliberate clinical use of sodium sulfate as a laxative)
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor:	ADI: 6 g sulfate/d (100 mg/kg_{bw}/d, 60 kg person)

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