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

4. Sodium

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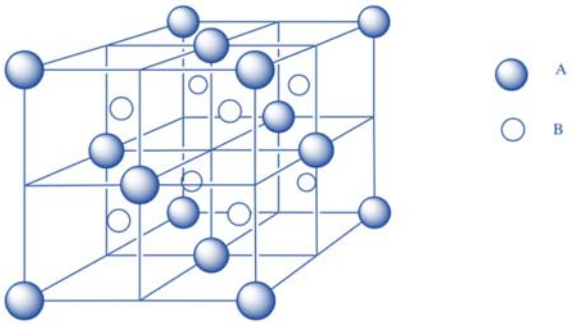

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Sodium: Brief profile on systemic toxicological effects

1. Identification

Name: sodium (cation)
Chemical formula: Na^+
Molecular mass: 22.99 g/mol

2. Introductory remarks

As an ion, sodium is not a substance under REACH, so that toxicological information is not available on the ion on its own. Sodium is a common cation, for example, in salts e.g. of halogens or (oxo)anionic metals. The aim of this summary on the systemic toxicity of sodium is to assist the assessor of health hazards of sodium containing substances, in determining whether the sodium moiety contributes to the overall toxicity of a substance. This document does not discuss primary literature or studies in great detail. Instead, reference is made to most recently published authoritative reviews, such as from the European Food Safety Authority. If no other citation is given, statements in this document have been directly copied or adopted from EFSA (2019).

3. Natural occurrence, physiological function and dietary intake

The sodium ion is naturally occurring and abundantly present in the environment (e.g. as part of the sodium chloride in seawater) and in the human body. Sodium has an essential function in human physiology as the dominant cation in extracellular fluids. The functions of sodium lie in (i) its participation in the control of the volume and systemic distribution of total body water, (ii) enabling the cellular uptake of solutes, and (iii) the generation of transmembrane electrochemical potentials via interactions with potassium. Sodium deficiency is rare and unlikely in healthy populations. Sodium chloride as well as other sodium salts are ubiquitous in the diet, and there are adaptive physiological mechanisms that reduce the losses of sodium in urine, faeces and sweat at low levels of sodium intake. Sodium chloride added during industrial or domestic food processing, and discretionary use for food preservation is the major source of dietary sodium in Western diets. The EFSA Panel has noted that the mean/median intake of sodium in the European adult populations exceeds the safe and adequate intakes set for sodium. The risk of inadequate (insufficient) intake in European populations is low. Concerns for European populations instead relate to excess intake of sodium.

4. Toxicokinetics

In healthy people, almost all dietary sodium is absorbed, even at very high level of intake. Following absorption, sodium ions are distributed by portal and systemic circulations, where their concentrations are maintained within a narrow range. Up to 95% of sodium body content is in the extracellular fluids, including a large proportion in bone, skin and muscle. The pool of sodium in bone, muscle and skin has been proposed to represent a sodium depot/reserve, but could also have a homeostatic and adaptive role as an extra-renal clearance depository for handling excessive systemic accumulation of sodium. The excretion and retention (i.e. homeostasis) of sodium is accomplished by an integrated neurohormonal control from centres located in the hypothalamus. The kidney is the main organ mediating the excretion and retention of sodium. It efficiently excretes sodium in response to high dietary intakes and salvages sodium when dietary intake is low. By contrast, sodium losses in the faeces are relatively stable and typically limited to a few mmol/d. The amount of sodium lost in sweat can vary widely, depending on, for example environmental conditions or the levels of physical activity (EFSA, 2019).

Toxicological effects

Based on its omnipresence and physiological function in humans, sodium in ionic form is not considered as "toxic" *per se*. However, health consequences of both chronic and acute deficiencies and excesses of sodium can occur, which are related to the distribution of total body water and sodium in the extracellular and intracellular fluid compartments. Due to the close interrelationship between sodium and chloride physiology and intakes, it is practically not possible to address standard toxicological data requirements for sodium on its own. The information in the subchapters below is therefore often based on the substance sodium chloride and provided for orientating purposes only. Key information regarding to the setting of safe intake levels of sodium is discussed in the sub-chapter on "repeated dose toxicity" and in the concluding remarks.

4.1. Acute toxicity

Rapid onset of sodium excess secondary to dietary sodium intake is uncommon, but acute toxicity may arise from high exposures to sodium, usually as sodium chloride, from ingestion (e.g. self-poisoning) or from parenteral administration in clinical care. Hypernatraemia, defined as a serum sodium concentration > 145 mmol/L, is typically a consequence of dehydration rather than of excessive sodium intake. The symptoms of hypernatraemia are similar to those of hyponatraemia and also include non-specific features such as headache, confusion, fever, nausea and vomiting (EFSA,2019). In animal studies on rats and mice with sodium chloride oral LD50 values of 3 - 5.8 g/kg_{bw} were found. There is no danger of poisoning following application to the skin (dermal LD50 on rabbits of > 10 g/kg_{bw}). Exposure to dust or mist from aqueous solutions of NaCl could lead to slight irritation in the nose and throat but there is no acute danger. The 1h LC50 for NaCl in an inhalation test on rats was above 42 000 mg/m^3 (Gestis, 2019).

4.2. Sensitisation

Experience and physiological knowledge indicate that NaCl does not cause sensitisation (Gestis, 2019). Thus, no sensitising properties are attributed to the sodium ion.

4.3. Repeated dose toxicity

The literature on the relationship between sodium intake and selected health outcomes, i.e. blood pressure, cardiovascular disease-related endpoints and bone health, has been systematically reviewed by EFSA (2019). To minimise the risk of bias in the evidence used in the assessment, the review was restricted to randomised controlled trials (RCTs) and prospective studies, studies that excluded participants with pre-existing medical conditions, and studies that used at least one 24-h urinary collection to estimate sodium intake.

Eligible studies on bone health provided limited and inconsistent evidence for an association between sodium intake and bone mineral density.

Regarding associations between sodium (quantified as urinary sodium "UNa") and coronary heart disease (CHD) and cardiovascular disease (CVD), EFSA concluded as follows:

- *There is some evidence for a positive association between UNa and risk of CHD. The positive relationship between UNa and blood pressure levels/incidence of hypertension, which is an established independent risk factor for CHD, supports this association.*
- *There is some evidence for an inverse association between UNa and risk of stroke. However, the number of eligible studies available investigating this outcome is small and the mechanisms by which UNa could be inversely associated with the risk of stroke are unclear,*

particularly considering the positive relationship between UNa and blood pressure, which is an established risk factor for stroke.

- *There is some evidence for a positive association between UNa and risk of total CVD, which is consistent with the evidence for a positive association between UNa and risk of CHD and the positive relationship between UNa and blood pressure levels/incidence of hypertension.*

4.4. Mutagenicity/genotoxicity

There are no indications that NaCl has any mutagenic effects. NaCl solutions of very low concentrations have been used as solvents for test substances in a variety of mutagenicity tests (because of their inactivity). Positive reactions found in isolated cases on cultivated mammalian cells or in microorganisms were probably caused by osmotic effects and are not attributable to mutagenicity by sodium or chloride (Gestis, 2019).

4.5. Reproductive toxicity

There are no indications that NaCl has any developmental toxic effects or influences fertility in humans. Epidemiological or animal studies on this using standardized methods are not available. In a limited study on rats, the offspring showed increased blood pressure when the mother received high NaCl doses in their drinking water (approx. 2 g/kg_{bw}) during pregnancies (Gestis, 2019, primary source not accessible).

4.6. Carcinogenicity

The EFSA Panel concluded that sodium itself was not carcinogenic but that high intakes of sodium chloride could increase susceptibility to carcinogens such as nitrosamines, gastric infection with Helicobacter pylori, or give inadequate protection against free radical-induced damage (EFSA, 2019).

5. Discussion and conclusion

EFSA (2019) recently provided a comprehensive overview of dietary reference values (adequate intakes) for sodium which have been set in the past by various authoritative bodies. For adults, such dietary reference values are typically in the range of approx. 1.5 – 2.5 g Na/d.

Overall, the EFSA Panel considered – in agreement with earlier assessments by others - that the available evidence cannot be used to determine the minimum sodium requirement in the population. Regarding a possible upper limit, the Panel considered that 2.0 g sodium/d is a safe and adequate intake for the general EU population of adults.

There is no evidence that the sodium requirement of lactating women differs from the requirement of non-lactating women. Sodium intakes considered safe and adequate for children were extrapolated from the value for adults, adjusting for their respective energy requirement and including a growth factor, and are as follows: 1.1 g/d for children aged 1–3 years, 1.3 g/d for children aged 4–6 years, 1.7 g/d for children aged 7–10 years and 2.0 g/d for children aged 11–17 years, respectively. For infants aged 7–11 months, an adequate intake of 0.2 g/d was proposed based on upwards extrapolation of the estimated sodium intake in exclusively breast-fed infants aged 0–6 months.

The EFSA Panel noted that the mean/median intake of sodium in the European adult populations exceeds the safe and adequate intakes set for sodium, and that efforts should be made to reduce sodium intake.

Sodium "in a nutshell":

Key / leading adverse systemic effect on human health:	Cardiovascular disease
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor:	An intake of 2 g Na/d is considered as safe for adults by EFSA, 2019, which corresponds to ca. 28.5 mg Na/kg_{bw}/d for a 70-kg person.

References

EFSA (2019): Dietary reference values for sodium. Adopted: 3 July 2019. doi:10.2903/j.efsa.2019.5778

Gestis (2019): GESTIS Substance Database. Information system on hazardous substances of the German Social Accident Insurance: https://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp [accessed 2019-07-04]