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

7. Chloride

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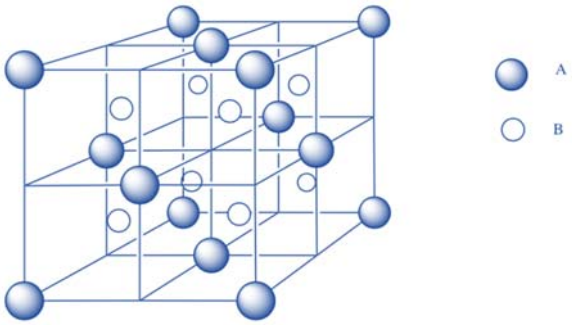

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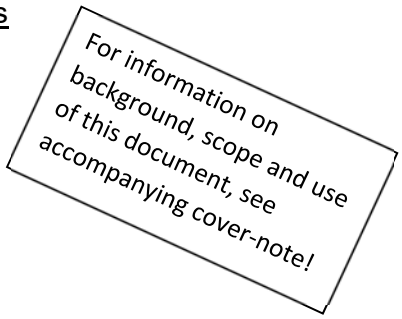
Chloride: Brief profile on systemic toxicological effects



1. Identification

Name: chloride (anion)
Chemical formula: Cl^-
Molecular mass: 35.453 g/mol

2. Introductory remarks

As an ion, chloride is not a substance under REACH, so that toxicological information is not available on the ion on its own. Chloride is a common anion in salts of cationic metals. The aim of this summary on the systemic toxicity of chloride is to assist the assessor of health hazards of chloride containing substances, in determining whether the chloride moiety contributes to the overall toxicity of the 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 either copied or adopted from EFSA (2019).

3. Natural occurrence, physiological function and dietary intake

Chloride is a naturally occurring anion which is abundantly present in the environment (e.g. as part of the sodium chloride in seawater) and in the human body. Chloride is the predominant anion in intracellular fluid and one of the most important extracellular anions. It contributes to many body functions including the maintenance of osmotic and acid–base balance, muscular and nervous activity, and the movement of water and solutes between fluid compartments. Reference serum chloride concentrations are in the range of 97 to 107 mmol/L (ca. 3.4 – 3.8 g /L). EFSA (2019) cites a paucity of publications providing estimates of daily chloride intake based on food consumption data, primarily reflecting limitations in capturing the intake of chloride sources (e.g. sodium chloride added at the table or in cooking) and the restricted knowledge of the chloride content of foodstuffs. Earlier estimates (EFSA, 2005) suggest that the mean daily chloride intakes of populations in Europe range from about 5-7 g (about 8-11g NaCl salt).

4. Toxicokinetics

In healthy people, chloride is efficiently absorbed in the gut. Following absorption, chloride anions are freely transported in the blood, where their concentration is maintained within a narrow range. Renal excretion of chloride is coupled primarily to that of sodium and potassium. The overall regulation of chloride balance is linked to that of sodium through hormonal control by the renin–angiotensin–aldosterone system and cortisol. The close interrelationship between sodium and chloride physiology and intakes are reflected by high correlations between sodium and chloride urinary excretion. Studies which quantified 24-hour urinary excretion of sodium and chloride in subjects from Western populations indicate that, on a molar basis, both electrolytes are excreted in similar amounts.

5. Toxicological effects

Due to the close interrelationship between sodium and chloride physiology and intakes, it is practically not possible to address standard toxicological data requirements for chloride on its own. The information in the subchapters below is therefore usually based on the substance sodium chloride and provided for orientating purposes only. The information is from authoritative secondary sources; and a detailed reliability assessment of the primary data has not been conducted when preparing this document. Please also refer to the discussion/conclusion below.

5.1. Acute toxicity

Main acute effects of NaCl are gastrointestinal and metabolic disturbances following oral intake of very high doses with secondary effects to the functions of organs. Oral LD_{50} values of 3 - 5.8 g/kg_{bw} were found in animal studies on rats and mice. There is no danger of poisoning following application to the skin (dermal LD_{50} on rabbits of > 10 g/kg_{bw}). Exposure to dust or mist from aqueous solutions could lead to slight irritation in the nose and throat but there is no acute danger. The 1h LC_{50} for NaCl in an inhalation test on rats was above 42 000 mg/m^3 (Gestis, 2019).

5.2. Sensitisation

Experience and physiological knowledge indicate that NaCl does not cause sensitisation (Gestis, 2019).

5.3. Repeated dose toxicity

There is evidence that chloride can contribute to the established effect of sodium chloride on blood pressure. However, as yet, mechanisms by which chloride on its own (independent of sodium) may have a direct effect on blood pressure, have not been established (EFSA, 2019).

5.4. 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 (Gestis, 2019).

5.5. 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).

5.6. Carcinogenicity

A number of prospective cohort studies have assessed the association between sodium chloride intake and gastric cancer incidence and/or mortality. The population- based studies available in the literature evaluated associations between sodium chloride or sodium intake and gastric cancer risk and *there are no studies that evaluated the independent role of chloride* from sodium chloride in the disease occurrence (EFSA, 2019).

6. Discussion and conclusion

EFSA (2019) has reviewed available data that would allow to derive dietary reference values for chloride, including an upper limit, above which adverse effects due to chloride would be observed.
The EFSA Panel noted the close relationship between sodium and chloride balances in the body, and concluded that there is insufficient data to assess toxicological effects (and to set an upper intake level) for chloride on its own. Only for the established effect of sodium chloride on blood pressure, EFSA states that there is evidence that chloride can contribute to the effect, although clear mechanisms by which chloride on its own may have a direct effect on blood pressure have not been established.

Further, similar urinary excretion levels of sodium and chloride (on a molar basis) are typically observed in Western populations. Hence, the EFSA Panel considers that reference values for chloride can be set at values equimolar to the reference values for sodium for all age and life-stage groups. Consistent with the values for sodium, the reference values proposed for chloride are considered to be safe[1] intakes for the general EU population, under the consideration that the main dietary source of chloride intake is sodium chloride.
For adults (> 18 years), including pregnant and lactating women, EFSA suggests a dietary reference level ("considered to be safe and adequate") of 3.1 g chloride per day. Thus, for the average adult with a default body weight of 70 kg a figure of 44 mg chloride/kg_{bw}/d can be adopted.

Chloride "in a nutshell":

Key / leading adverse systemic effect on human health:	Possible but not proven contribution of chloride on adverse effects on blood pressure by sodium chloride.
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor:	dietary reference level ("considered to be safe and adequate"): 44 mg chloride/ kg_{bw} / d for adults

References

EFSA (2005) Scientific Opinion of NDA Panel: Opinion of the Scientific Panel on Dietetic products, nutrition and allergies [NDA] on a request from the Commission related to the Tolerable Upper Intake Level of Chloride (Question No EFSA-Q-2003-018), The EFSA Journal, 210, 1-9

EFSA (2019): Dietary Reference Values for chloride. Draft for public consultation. Retrieved on 2019-07-04 from
https://www.efsa.europa.eu/sites/default/files/consultation/consultation/190403_Draft_opinion_DRV_for_chloride.pdf

1 The concept of a *safe* intake has been used in previous assessments by EFSA when providing advice on a daily intake of a nutrient which does not give rise to concerns about adverse health effects, in case a tolerable upper intake level (UL) could not be established.

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]