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

1. Calcium

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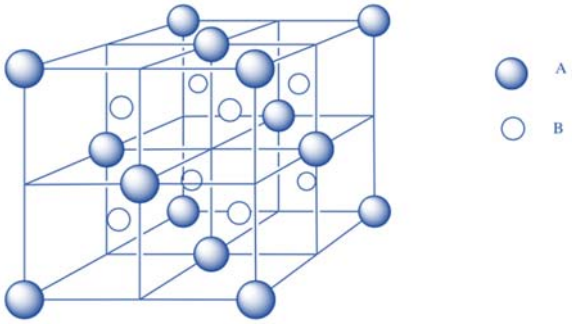

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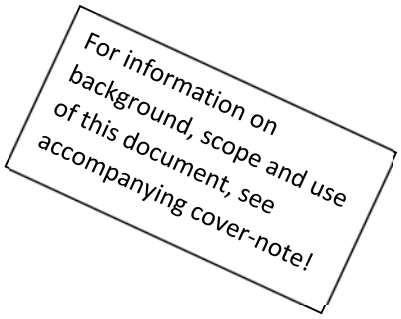
Calcium: Brief profile on systemic toxicological effects



1. Identification

Name: calcium (cation)
Chemical formula: Ca^{2+}
Molecular mass: 40.1 g/mol

2. Introductory remarks

In the form of a divalent cation, calcium is not a substance under REACH, so that toxicological information is not available on the ion on its own. Calcium is a common cation in many salts containing inorganic anions, oxoanions or organic anionic moieties. The aim of this summary on the systemic toxicity of calcium is to assist the assessor of health hazards of such calcium containing substances, in determining whether the calcium 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. Unless stated otherwise, EFSA (2012 and 2015) is the source of the information summarised in this document.

3. Natural occurrence, physiological function and dietary intake

Calcium as a nutrient is most commonly associated with the formation and metabolism of bone. Over 99 % of total body calcium is found as calcium hydroxyapatite in bones and teeth, where it provides hard tissue with its strength. In addition, calcium acts as an important intracellular messenger in cells and tissues. It has a critical role in many physiological functions involved in the regulation of metabolic processes, including vascular contraction and vasodilation, muscle contraction, enzyme activation, neural transmission, membrane transport, glandular secretion and hormone function. Calcium is known for its U-shaped dose- response relationship, which means that both too low as well as excess intake of calcium can result in adverse effects on human health. Human serum calcium levels are regulated within a narrow range (2.2 to 2.6 mmol/L) by three main calcium-regulating hormones.
Calcium deficiency (hypocalcemia) is rare but can be induced by some diseases and also by certain drugs. Acute effects of hypocalcemia can result for example in muscle spasms/muscle stiffness or seizures. Most of the adverse effects of chronic hypocalcemia are linked to the skeleton. Calcium is then resorbed from the skeleton to maintain blood concentrations within the range required for normal cellular and tissue functions. This causes a reduction in bone mass, which leads to a lower than normal bone mineral density and osteoporosis, associated with an increased risk of fracture.
The main dietary sources of calcium vary, although dairy products are generally the most important food group. Water may also contribute significantly to the daily intake in hard water areas. A large database of studies investigating actual dietary intakes of calcium exist from various countries and age groups. EFSA (2015) has evaluated the data and noted a rather high variability of intake estimates. As an example, estimates for average calcium intake varied from 690 to 1122 mg/day for adults between different studies. For details, also on other age groups, see EFSA (2015).

4. Toxicokinetics

Calcium salts such as carbonate dissociate into their constituent ions in the acid milieu of the stomach. Some of the calcium is absorbed, via active transport or passive diffusion, the bulk (89-90%) of unabsorbed calcium is complexed to bile acids, free fatty acids and oxalic acid and excreted with the faeces. Absorption of calcium from calcium carbonate in rats and humans is comparable to that from calcium citrate malate, average absorption of calcium from calcium carbonate over a range of studies being in the range of 20-40% (EFSA, 2011). Calcium is subject to tight homeostasis in humans, which is under endocrine and genetic control.

Systemic and local factors regulate intestinal absorption, influx and efflux from bone, and calcium excretion and re-absorption by the kidney. Intestinal calcium absorption occurs through both an active, saturable, transcellular process and a non-saturable, passive process. Active transport is controlled by 1,25(OH)2D, the principal hormonal form of vitamin D, whereas passive transport is paracellular. Calcium absorption varies considerably throughout the lifespan, being higher during periods of rapid growth and lower in old age. Calcium absorption is affected by vitamin D status; it has been shown to be low in patients with vitamin D deficiency, but there is uncertainty about the serum concentration of 1,25(OH)D that is required for optimal calcium absorption (EFSA 2012, 2015).

5. Toxicological effects

Calcium is a ubiquitous, essential nutrient which is involved in many human physiological functions and is generally considered as non-toxic. Available toxicity information is not for the calcium moiety on its own, but refers to various calcium substances. It is usually difficult to quantify the contribution of the calcium moiety to the observed toxicity. The solubility of the substances, the respective counterions and also possible local effects can contribute.

5.1. Acute toxicity

The acute toxicity of calcium salts is low. A large database of studies in various animal species and via different routes of exposure is available, e.g. in factual databases such as the HSDB or RTECS. For the sake of brevity, only the following acute oral LD_{50} in rats for three calcium salts are presented here:

Substance	LD50, oral, rat in mg/kg	Reference
Calcium acetate	4280	RTECS (2010)
Calcium chloride	3798 - 4179	OECD (2002)
Calcium sulfate	> 5000	OECD (2009)

5.2. Sensitisation

Given that calcium is a ubiquitous, essential nutrient which is involved in many human physiological functions, it is justified to assume that calcium does not have sensitising properties. This topic is not addressed by EFSA, probably due to a lack of relevance. The OECD SIDS for calcium chloride and -sulfate (references in the table above) likewise indicates that no data on skin sensitisation is available for these substances.

5.3. Repeated dose toxicity

A number of potential adverse effects of highly excessive calcium intakes have been proposed. These include hypercalciuria, deterioration of kidney function, kidney stone formation, the milk-alkali syndrome (MAS), vascular calcification, increased risk of cardiovascular disease and increased risk of prostate cancer. The SCF (2003) based the derivation of it upper limit (UL) for calcium on the evidence of different intervention studies of long duration, some of which were placebo controlled, in which total daily calcium intakes of 2,500 mg from both diet and supplements were tolerated without adverse effects. Because of the abundance of data, the application of an uncertainty factor was considered unnecessary. A UL of 2,500 mg of calcium per day from all sources was proposed for adults, and for pregnant and lactating women. When reviewing the literature in 2012 and 2015, the EFSA Panel concludes that no new data have become available which would require a revision of this UL for calcium for adults, including pregnant and lactating women, and that no new data have become available which would allow the setting of a UL for infants, children or adolescents.

5.4. Mutagenicity/genotoxicity

Given that calcium is a ubiquitous, essential nutrient which is involved in many human physiological functions, it is justified to assume that calcium does not have mutagenic properties. This topic is not addressed by EFSA, probably due to a lack of relevance. The REACH registration dossier on calcium

chloride refers to a published study in which calcium chloride was negative in bacterial reverse mutation tests and in a mammalian chromosome aberration test (Ishidate et al., 1984). Likewise, all genotoxicity studies on calcium chloride considered as reliable (with or without restrictions) by OECD (2002) were negative.

5.5. Reproductive toxicity

Calcium is a ubiquitous, essential nutrient which is involved in many human physiological functions, and highly efficient homeostasis takes places in humans, including the increase of absorption and a more efficient transport in times of increased need for calcium e.g. during growth, pregnancy and lactation. Adverse effects on reproduction and development are not expected.

In experimental animals, prenatal developmental toxicity studies in rats, mice and rabbits have been performed with calcium chloride that were equivalent to OECD TG 414, although the study was conducted before the establishment of the guideline (OECD, 2002, original studies performed in 1974). No toxic effects of calcium chloride on dams or fetuses were observed at doses up to 189 mg/kg_{bw}/d (mouse), 176 mg/kg_{bw}/d (rat) and 169 mg/kg_{bw}/d (rabbit). These were the highest doses tested (representing unbounded NOAELs).

5.6. Carcinogenicity

The majority of epidemiological studies and the few randomised control trials (RCTs) which have reported cancer as an outcome found either an inverse or no association between calcium intakes from food and/or supplements and the risk of cancer (incidence and mortality), with the exception of some studies linking excess calcium intake (> 1000 mg/day) with increased risk for prostate cancer. When reviewing these data, EFSA (2012) noted that these studies were uncontrolled for factors other than calcium and which may have been responsible for the effect, and that the only RCT which reported on this outcome showed no effect of calcium supplementation at doses of 1,200 mg/day (up to about 2,000 mg/day of total calcium) on the risk of prostate cancer. Thus, the upper limit set by SCF of 2,500 mg/day was upheld.

6. Discussion and conclusion

Calcium is a ubiquitous, essential nutrient which is involved in many human physiological functions and is generally considered as non-toxic. Calcium is subject to efficient homeostasis in humans, which is under endocrine and genetic control. Nevertheless, a number of potential adverse effects of highly excessive calcium intakes have been proposed. These include hypercalciuria, deterioration of kidney function, kidney stone formation, the milk-alkali syndrome (MAS), vascular calcification, increased risk of cardiovascular disease and increased risk of prostate cancer. The SCF (2003, confirmed by EFSA, 2012 and 2015) based the derivation of its upper limit (UL) for calcium on the evidence of different intervention studies of long duration, some of which were placebo controlled, in which total daily calcium intakes of 2,500 mg from both diet and supplements were tolerated without adverse effects. Because of the abundance of data, the application of an uncertainty factor was considered unnecessary. A UL of 2,500 mg of calcium per day from all sources was proposed for adults, and for pregnant and lactating women. No data have become available which would allow the setting of a UL for infants, children or adolescents.

Calcium "in a nutshell":

Key / leading adverse systemic effect on human health:	See discussion and conclusion
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor:	Upper limit of intake from all sources for adults: 2,500 mg Ca/day (SCF, 2003; EFSA, 2015). Corresponds to ca. 36 mg Ca/kg_{bw}/d for a 70-kg adult

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