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

9. Carbonate

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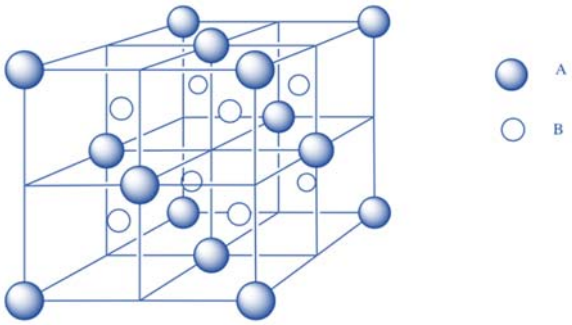

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Carbonate: Brief profile on systemic toxicological effects

1. Identification

Name: (hydrogen)carbonate (anions)
Chemical formula: CO_3^{2-}, HCO_3^-
Molecular mass: 60.01 g/mol (61 g/mol for HCO_3^-)

2. Introductory remarks

As an ion, carbonate is not a substance under REACH, so that toxicological information is not available on the ion on its own. Carbonate is a common anion in salts of cationic metals. The aim of this summary on the systemic toxicity of carbonate is to assist the assessor of health hazards of such carbonate containing substances, in determining whether the carbonate 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, such as from the European Food Safety Authority.
Several carbonate salts are approved in the EU as food additives (Regulation (EU) No 1129/2011) with no specific quantity restriction (*quantum satis*): calcium carbonate (E170), sodium carbonate (E500), potassium carbonate (E501), ammonium carbonate (E503) and magnesium carbonate (E504). Further, a dossier on sodium hydrogen carbonate has been submitted for approval as an *active substance* in plant protection products in accordance with Regulation (EC) 1107/2009 under which the same substance is already approved as a *basic substance*. A Draft Assessment Report (DAR) is available [EC, 2017].

3. Natural occurrence and physiological function

Carbon is the primary component of all life on earth as well as a major component of many minerals such as limestone. In the so-called carbon cycle, carbon is exchanged among the biosphere, pedosphere, geosphere, hydrosphere, and atmosphere. Part of this cycle is the formation of carbonate, CO_3^{2-}, an inorganic anion which is formed in all aerobic organisms during the process of aerobic respiration and therefore is a natural constituent of man, animals and plants. The high capacity of the buffer system carbonic acid/hydrogen carbonate/carbonate plays an important role in maintaining a constant pH in blood plasma.

4. Toxicokinetics

In the human body, “carbonate” speciation largely depends on pH, according to the following equilibrium equation:

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+ \quad (\text{or } “H_2CO_3”) \leftrightarrow CO_3^{2-} + 2\ H^+$$

Based on this equation, CO_2 is the predominant species at a pH lower than 6.35, while HCO_3^- being the predominant species at pH 6.35 – 10.33, and CO_3^{2-} is predominant at pH>10.33. This equation describes the reactions that are responsible for the buffering capacity of the $CO_2/HCO_3^-/CO_3^{2-}$ system, which helps to maintain the pH of human blood plasma at 7.4. The human body maintains homeostatic mechanisms to ensure required pH conditions in bodily fluids and organs. Excess CO_2 can be exhaled whereas excess carbonate or hydrogencarbonate ions are cleared by the renal system [EC, 2017].

5. Toxicological effects

Given that carbonate is ubiquitous in nature as part of the geochemical carbon-cycle, and due to its essential involvement in physiological functions in humans, carbonate is generally considered as non-toxic. For the sake of completeness, some information is presented below on each formal REACH data requirement on toxic effects. Usually the information is not for the carbonate ion/moiety on its own, but in fact based on carbonate salts. If any toxicological effects are observed, these are usually attributable to the non-carbonate-moeity of the substance even when these are also considered as of low toxicity. For example, the EFSA assessment of calcium carbonate [EFSA, 2011] largely refers to effects of calcium for which there is also an ADI. Similarly, a safety assessment of ferrous carbonate for its use in feed additives for animals focussed on the iron moiety, rather than the carbonate [EFSA, 2015].

5.1. Acute toxicity

The acute toxicity of carbonates is very low with LD50 values generally exceeding 4,000 mg/kg bw for sodium hydrogen carbonate, as summarised in the DAR on this substance [EC, 2017], which cites studies from an OECD SIDS dossier (OECD, 2002).

5.2. Sensitisation

Not considered relevant for carbonate, based on its ubiquitous presence and involvement in physiological functions and no reports of sensitising effects despite long-term historical and wide dispersive industrial and consumer uses of carbonates (e.g. the construction industries, in the making of iron in blast furnaces, as fillers in plastics, as extender in paints, as chalk…).

5.3. Repeated dose toxicity

Few existing sub-chronic toxicity studies have been summarised in the DAR on sodium hydrogen carbonate (EC, 2017), with the key reference being Lina and Kuijpers (2004). The authors assessed the toxicity and carcinogenicity of acidogenic or alkalogenic diets in rats, with potassium hydrogen carbonate acting as the test item added to the diet to alkalize the urine of the animals. EC (2017) summarised the finding from this study as follows: *"The finding showed that hyperplasia of the bladder epithelium of rats can be induced both by acidifying and by alkalizing the urine through manipulation of the acid-base balance of the basal diet through excess of either NH_4Cl or $KHCO_3$."* For a further discussion, see section on carcinogenicity below.

5.4. Mutagenicity/genotoxicity

There are no studies indicating any genotoxic potential of carbonates, which is not surprising given its essential involvement in physiological processes such as pH regulation. Some studies on sodium- or potassium hydrogen carbonate have been considered by EC (2017), citing from OECD (2002). Although these studies were usually not conducted in accordance with guidelines, they are more or less well documented. All these studies, including Ames test, chromosome aberration test, a DNA repair assay and a reverse mutation assay were negative.

5.5. Reproductive toxicity

The DAR on sodium hydrogen carbonate (EC, 2017) considers that the substance is not a reproductive toxin since humans are exposed to high background levels in nature and since the resulting ions including (hydrogen)carbonate are of physiological importance. Rather old oral teratogenicity studies in mice and rabbits, as cited from FDA (1975) were negative. EC (2017) further considers the long-term and wide use of such carbonates as food additive and in over-the-counter drugs, as well its low acute and short-term toxicity and absence of genotoxicity, in reaching the conclusion that further studies on reproductive toxicity are not required.

5.6. Carcinogenicity

Sodium hydrogen carbonate was reviewed in the OECD SIDS programme (OECD, 2002), concluding that the substance has no carcinogenic effect.

Some sub-chronic or chronic toxicity and/or carcinogenicity studies highlight promoting properties on urinary bladder cancer of carbonate salts such as $KHCO_3$ at relatively high concentrations in the feed (ca. 0.375 – 3 %). EC (2017) also states that sodium and potassium salts of various anions have been shown to be non-genotoxic promoters of bladder carcinogenesis in rats, particularly in males. These results are consistent with a non-genotoxic mechanism for bladder cancer in rats. The mechanism involves long-term elevation of urinary pH, formation of precipitates and calculi resulting in damage to transitional epithelial cells, subsequently leading to regenerative proliferation. Male rats are considered to be more sensitive towards this effect, due to their elevated protein content in the urine compared to females. This epigenetic mechanism was shown to be dose-dependent with a clear threshold. No other neoplastic effects in other organs were seen in the studies with KHCO3. In conclusion, as described by WHO (1999), this mechanism is not considered relevant for humans.

6. Discussion and conclusion

Carbonates are ubiquitous on earth, omnipresent in the human diet, and involved in essential physiological function, most importantly because of the buffer system $CO_2/HCO_3^-/CO_3^{2-}$. Long-term alkalization of the urine in rats and only at very high, repeated doses has been considered to contribute to urinary bladder cancer in this species, but this mechanism is not considered relevant for humans. In conclusion, carbonate is not considered as of any toxicological concern for humans.

Carbonate "in a nutshell":

Key / leading adverse systemic effect on human health:	none
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor	No DNEL or similar threshold like ADI or UL can be established for carbonate. Carbonates are omnipresent in the environment, including in the diet. Several carbonate salts are approved in the EU as food additives (Regulation (EU) No 1129/2011) with no specific quantity restriction (*quantum satis*), and likewise considers GRAS substances (Generally Regarded as Safe) by US FDA.

References

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