

Risk Assessment

Sodium chloride

General information

No relevant data are available relating to the toxicity of the chloride ion, and therefore the EVM decided to consider sodium chloride as a salt, rather than the separate elements. SACN is currently considering salt intakes and health as part of a review and their recommendations are due to be published later this year.

Chemistry

Sodium chloride is the simple ionic salt of sodium and chlorine. It is an odourless clear or white soft crystal with a distinctive taste.

Natural occurrence

Sodium chloride occurs naturally as halite, known as rock salt, which is typically 95 to 99% sodium chloride. The principal impurity of rock salt is calcium sulphate, with smaller amounts of calcium chloride and magnesium chloride.

Occurrence in food and food supplements

The salt content of natural foods varies widely. The main sources of sodium intake (excluding table salt) in the British diet are cereals and cereal products (particularly bread) and meat and meat products. Crisps and savoury snacks tend to be high in salt and can make a significant contribution to sodium intakes. The main sources of chloride are the same as for sodium. The majority of salt intake in the UK diet comes from processed foods, with about 10% from the natural salt content of unprocessed foods.

Other sources of exposure

No data were identified.

Recommended amounts

In adults, the RNI for sodium is 1600 mg/day and for chloride 2500 mg/day. COMA recommended a reduction in the average intake of sodium chloride from food by the adult population from the current level of 9000 mg/day (150 mmol/day) to 6000 mg/day (100 mmol/day) (COMA, 1994).

Analysis of tissue levels, sodium and chloride status

The steady-state concentrations of sodium and chloride in mammalian skeletal muscle are 12 mmol per litre and 3.8 mmol per litre in the intracellular fluid respectively and 145 mmol per litre and 120 mmol per litre in the extracellular fluid respectively. In nerves, depolarisation is a manifestation of Na⁺ influx. Serum sodium levels are well maintained at approximately 140 mmol per litre even in studies involving high or low salt diets and elderly subjects.

Brief overview of non-nutritional beneficial effects

Sodium chloride is an essential nutrient for the normal functioning of the body. It is important for nerve conduction, muscle contraction, correct osmotic balance of extracellular fluid and the absorption of other nutrients.

Function

Sodium, together with potassium, is an essential mineral for regulating body fluid balance. Sodium is the most abundant cation in the extracellular fluid and sodium salts account for more than 90% of the osmotically active solute in the plasma and interstitial fluid. Consequently, sodium load is the major determinant of extracellular volume. Chloride is also important in maintaining the fluid balance and is an essential component of the gastric and intestinal secretions.

Deficiency

Sodium deficiency is highly unusual, but can lead to low blood pressure, dehydration and muscle cramps. A normal diet will always supply sufficient chloride.

Interactions

Patients on salt restricted diets who also take lithium carbonate, prescribed for the treatment of manic disorders, are susceptible to development of lithium toxicity. The excretion of lithium appears to be proportional to the intake of sodium and increased sodium intake can reduce both therapeutic responses to lithium and its side effects.

Absorption and bioavailability

Sodium is absorbed passively from the lumen of the entire length of the intestine. Chloride is also absorbed passively, but with decreasing efficiency along the length of the intestine and is not absorbed at all in the colon. Ionic sodium can also be absorbed actively from the lumen of the small intestine and colon. Once in the intestinal epithelium it is actively transported to the interstitial fluid.

Distribution and metabolism

Sodium is the principal cation of the plasma.

Excretion

Under normal conditions, gastrointestinal and respiratory excretion of sodium is negligible and sodium is excreted primarily by the kidneys. Chloride excretion is by passive diffusion, but it also leaves the tubular lumen by active transport.

Toxicity

Human data

Although rare, acute toxicity may be caused by ingestion of 500 – 1000 mg sodium chloride/kg body weight. Symptoms include vomiting, ulceration of the gastrointestinal tract, muscle weakness and renal damage, leading to dehydration, metabolic acidosis and severe peripheral and central neural effects.

Opinion is divided concerning the long-term influence of dietary sodium chloride intakes greater than 6000 mg per day, on the development of essential hypertension. Significant increases in both systolic and diastolic blood pressures have been shown in studies in which normotensive adults have received supplementary sodium. Reduction of dietary sodium is generally recommended as a non-pharmacological treatment for patients with essential hypertension. In normotensive adults a significant reduction in sodium intake is needed to achieve a modest reduction in blood pressure. In hypertensive patients, the most pronounced effects of dietary salt restriction have been shown to be in people aged greater than 44 years. Left ventricular hypertrophy, an important risk factor in premature cardiovascular disease, appears to be associated with high dietary sodium.

High sodium chloride intakes increase calcium excretion and may increase the risk of kidney stone formation. However, there is no substantial evidence to suggest a relationship between excess sodium chloride intake and reduced bone mineral density.

Animal data

Unilaterally nephrectomised rats treated with deoxycortisone acetate (DOCA) are used as a salt-sensitive model of hypertension, whereas two kidney one clip (2K1C) rats are used as a salt-resistant hypertensive model. Using these models it has been shown that high dietary sodium chloride (21% in chow) significantly increased systolic blood pressure in DOCA treated rats, but not in controls or 2K1C rats. The high salt diet exacerbated renal arterial and arteriolar and glomerular lesions in both the salt-dependent and salt-independent hypertension models. *Ad libitum* feeding of rats with diets containing sodium chloride or sodium citrate, or sodium-free diet, for four weeks showed that dietary sodium restriction prevented the development of left ventricular hypertrophy.

Reproductive toxicity

In rodents, extremely high doses of sodium chloride during pregnancy caused musculoskeletal abnormalities, foetotoxicity and foetal death and post-implantation mortality and abortion. High dietary sodium chloride intakes throughout gestation and during the early life of offspring have been shown to predispose to high fluid retention in the rat. Administration of a high sodium chloride diet from conception to weaning increased adult blood pressure, whereas exposure only at weaning had no effect on blood pressure. Rats born to mothers on a normal sodium diet, but fed by females on a high sodium diet, and then weaned and raised on a high sodium diet, developed more hypertension than those only raised on a high sodium diet after weaning. Thus it appears that the transfer of sodium via maternal milk is an important factor in the development of high blood pressure in adult rodents.

Carcinogenicity and genotoxicity

Sodium chloride has been demonstrated to be a gastric tumour promoter in experimental animals and high sodium chloride intakes have been associated with incidence of stomach cancer in human populations with traditional diets of highly concentrated, salted foods.

Vulnerable groups

It has been suggested that the blood pressure of some individuals is far more sensitive to the effects of sodium depletion or loading than others. These individuals are considered to be salt-sensitive. In a normotensive population (320 subjects) approximately 30% were shown to be salt-sensitive, irrespective of ethnic origin. Characteristics shared by 'salt-sensitive' individuals include differences in responses of the renin-angiotensin and sympathetic nervous systems, renal function, body fat distribution, insulin resistance and intracellular ion transport.

Since urinary calcium excretion increases with elevated dietary sodium chloride (by approximately 1 mmol calcium (40 mg) for each 100 mmol (2300 mg) increase in sodium chloride), high salt intake increases susceptibility to calcium salt crystallisation in urine. In calcium stone-forming patients, high sodium chloride intake has been associated with low bone density.

Very young babies cannot excrete excess sodium chloride through their kidneys, which gives rise to the advice that salt should not be added to baby foods.

Genetic variations

It has been shown that in a hypertensive population in the USA, 73% of black people were salt-sensitive, compared with 55% of white people. An increase in salt sensitivity with increasing age and at lower renin levels appears to be common in the three ethnic groups most commonly studied (whites, blacks and Japanese). Compared with white populations, black populations have higher blood pressure earlier in life and have a greater incidence of more severe hypertension and thus a greater risk of cardiovascular complications. Considering hypertension and associated cardiovascular complications, males are a higher risk group than females.

Mechanism of toxicity

Experiments in salt-sensitive rats indicate that increased blood pressure results initially from a combination of increased cardiac output and total peripheral resistance.

Dose response characterisation

The effect of sodium chloride on hypertension is a continuous response with no threshold. Susceptible people are affected at intakes that would not cause an effect in the rest of the population. Blood pressure is linked to salt consumption, and the magnitude of the increase in blood pressure is linked to age.

Studies of particular importance in the risk assessment:

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD)

Human data

Mascioli et al., 1991

In a randomised, double-blind cross-over trial normotensive subjects (n = 48, average age 52 years) were placed on a low sodium basal diet (35 mmeq sodium/day or less, approximately 800 mg sodium/day). After six weeks acclimatisation this group received capsules containing supplementary sodium chloride (96 mmeq sodium/day, approximately 2200 mg sodium/day) for four weeks. They then entered a two-week washout phase, followed by a four-week placebo period. A second group had a four-week placebo period first, then a two-week washout period, which was followed by four weeks of sodium chloride capsules. Total sodium chloride intake during the treatment period was estimated to be approximately 7500 mg/day. On average, both systolic and diastolic blood pressures increased significantly (3.6/2.3 mm Hg) during the sodium chloride treatment periods, compared with the placebo control. Increases in systolic and diastolic blood pressure were recorded in 65% and 69%, respectively, of study participants during the sodium chloride treatment period, compared with the placebo control.

Ganry et al., 1993

A small crossover study, of six normotensive patients (males and females), examined the effect of sodium chloride or sodium bicarbonate on blood pressure regulation. The subjects were given a basal diet containing 85 mmol sodium chloride and each of the two treatments gave an additional 151 mmol sodium per day for six days with similar water intake. Additional sodium chloride was given in the form of nine capsules, 9 x 986 mg = 8,874 mg/day, leading to a total sodium chloride intake of approximately 13,900 mg/day. Sodium loading in the form of bicarbonate had no effect on blood pressure, whereas sodium chloride for the same period significantly increased the blood pressure.

Exposure assessment

Total exposure/intake:

Food	Mean: 7200 mg/day 97.5 th percentile: 13000 mg/day (from 1986/1987 NDNS)
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Note 1: this does not include salt added at the table or during cooking.

Note 2: Supplements do not contain sodium chloride, but some contain chloride at up to 72 mg/daily dose.

Estimated maximum daily intake: 13000 mg/day

No potential high intake groups have been identified.

Risk assessment

Although rare, acute sodium chloride toxicity may be caused by ingestion of 500 – 1000 mg sodium chloride/kg bodyweight. Symptoms include vomiting, ulceration of the gastrointestinal tract, muscle weakness and renal damage, leading to dehydration, metabolic acidosis and severe peripheral and central neural effects. This is however, normally self-limiting.

High sodium chloride intakes increase calcium excretion and may increase the risk of kidney stone formation. There is evidence for a causal relationship between the consumption of sodium (mainly from common salt) and both blood pressure and the age-related rise in blood pressure. Data suggest that 30% of a normotensive population may be salt sensitive.

In rodents, extremely high doses of sodium chloride during pregnancy caused musculoskeletal abnormalities, foetotoxicity and foetal death and post-implantation mortality and abortion. Administration to rats of diets containing high levels of sodium chloride throughout pregnancy and during the early life of offspring have been shown to permanently alter fluid retention and to increase blood pressure in the offspring.

EVM OPINION

It is not possible to establish a Safe Upper Level for sodium chloride because there appears to be a graded response across doses that include the current estimated intake in the UK.

Increased blood pressure is seen in susceptible sectors of the population (those who are 'salt sensitive'), at intake levels that are not above average for the population as a whole. Results are available from numerous trials in hypertensive individuals, in which decreasing sodium chloride intake has been shown to have beneficial effects, by lowering blood pressure. However, the data from administration of increased levels of dietary sodium chloride are minimal. Opinion is divided concerning the long-term influence of dietary sodium chloride intakes greater than 6000 mg per day on the development of essential hypertension. Increases in both systolic and diastolic blood pressures were observed in normotensive adults receiving 2200 mg/day supplementary sodium, with estimate total sodium chloride intake of 7500 mg/day. Two small trials in normotensive individuals have shown that intakes of sodium chloride of approximately 14,000 mg/day lead to increased blood pressures. The assumption is made that similar or greater effects might follow augmentation of sodium chloride intake in hypertensive individuals.

Sodium chloride causes an increase in blood pressure at customary dietary intakes in susceptible individuals, leading to the COMA and SACN recommendations for a reduction in intake. Sodium chloride is not ordinarily suitable for use in supplements.

References

COMA (1994). Nutritional Aspects of Cardiovascular Disease. Report of the Cardiovascular Review Group, Committee on Medical Aspects of Food and Nutrition Policy. HMSO, London.

Ganry O., Boudet J., Wargon C., Hornych A. and Meyer P. J. (1993) Effect of sodium bicarbonate and sodium chloride on arterial blood pressure, plasma renin activity and urinary prostaglandins in healthy volunteers. *Journal of Hypertension* 11 (suppl 5), S202-S203.

Mascioli S., Grimm Jr. R., Launer C., Svendsen K., Flack J., Gonzalez N., Elmer P. and Neaton J. (1991) *Hypertension* 17 (suppl. 1), 1-21-1-26.