Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Chloride

(Request N° EFSA-Q-2003-018)

(adopted on 21 April 2005)

SUMMARY

Chloride is an essential nutrient involved in fluid and electrolyte balance and is required for normal cellular function. Dietary deficiency of chloride is very uncommon due to the widespread occurrence of chloride in foods.

Chloride is present in foods as a normal constituent at a low level. It is also added to foods, mainly as sodium chloride (commonly known as salt) or as mixtures of sodium chloride and potassium chloride (sometimes referred to as salt substitutes) during processing, cooking and immediately prior to consumption. The main reasons for the addition of salt during the processing of foods are for flavour, texture and preservation.

Mean daily chloride intakes of populations in Europe range from about 5-7 g (about 8-11g salt) and are well in excess of dietary needs (about 2 - 2.5 g chloride/day in adults). The main source of chloride in the diet is from processed foods (about 70-75% of the total intake), with about 10-15% from naturally occurring chloride in unprocessed foods and about 10-15% from discretionary chloride added during cooking and at the table.

The major adverse effect of increased intake of chloride, as sodium chloride, is elevated blood pressure. Higher blood pressure is an acknowledged risk factor for ischaemic heart disease, stroke and renal disease which are major causes of morbidity and mortality in Europe. For groups of individuals there is strong evidence of a dose dependent rise in blood pressure with increased consumption of chloride as sodium chloride. This is a continuous relationship which embraces the levels of chloride habitually consumed and it is not possible to determine a threshold level of habitual chloride consumption below which there is unlikely to be any adverse effect on blood pressure.

Gastrointestinal symptoms (discomfort, mucosal lesions and sometimes ulceration) have been seen in healthy subjects taking some forms of potassium chloride supplements (e.g. slow-release, wax matrix formulations) with doses ranging from about 1 to 4 g chloride per day, or more, but incidence and severity seem to be more dependent on the formulation than on dose.

Chloride is not carcinogenic but high intakes of sodium chloride can increase the susceptibility to the carcinogenic effects of carcinogens, such as nitrosamines, and gastric infection with *H. pylori*.

The panel concludes that the available data are not sufficient to establish an UL for chloride from dietary sources.

There is strong evidence that the current levels of chloride consumption (as sodium chloride) in European countries contribute to increased blood pressure in the population, which in turn has been directly related to the development of cardiovascular disease and renal disease. For this reason, a number of national and international bodies have set targets for a reduction in the chloride as sodium chloride consumed in the diet.

KEY WORDS

Chloride, salt, blood pressure, tolerable upper intake level, food safety.

BACKGROUND

In 2002, the European Parliament and the Council adopted Directive 2002/46/EC[1] related to food supplements containing vitamins and minerals.

In addition, and as announced in its White Paper on Food Safety, the Commission aims to put forward a proposal for harmonising legislation concerning the addition of vitamins and minerals to foods.

With a view to provide scientific support to the European Commission's legislative work in this field, the Scientific Committee on Food (SCF) issued, from October 2000 to April 2003, a series of opinions on tolerable upper intake levels of individual vitamins and minerals and safety factors in relation to their use in fortified foods and food supplements (available on the Internet at: http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html).

The SCF opinions covered 22 out of the 29 nutrients, which were considered to be within their mandate for this task. The SCF did not have sufficient time to adopt opinions for the following vitamins and minerals: vitamin C, chloride, fluoride, iron, phosphorus, potassium and sodium. In addition, during the decision making process for the adoption of Directive 2000/46/EC on food supplements the Parliament requested that boron, nickel, silicon, vanadium and tin should be allowed to be used in food supplements. Therefore, the European Food Safety Authority is asked to provide scientific opinions on the remaining 12 vitamins and minerals in accordance with the present terms of reference.

TERMS OF REFERENCE

With respect to the outstanding 12 vitamins and minerals, the European Food Safety Authority is asked 1) to review the upper levels of daily intakes that are unlikely to pose a risk of adverse health effects; 2) to provide the basis for the establishment of safety factors, where necessary, which would ensure the safety of fortified foods and food supplements containing the aforementioned nutrients.

[1] Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements. OJ L 183. 12.7.2002, p. 51.

ASSESSMENT

1. INTRODUCTION

Chloride is found widely in nature and as a normal constituent of foods, generally as salts of sodium (NaCl) or potassium (KCl). Chloride is also added to food mainly as sodium chloride (commonly known as salt (1 mmol is equivalent to 35.5 mg chloride and approximates 58 mg sodium chloride) or mixtures of sodium chloride and potassium chloride (sometimes referred to as salt substitutes). Other chloride salts may be added, generally at lower amount, to food for nutritional or technological purpose, e.g. magnesium chloride. Ammonium chloride is permitted to be added to certain foods (e.g. liquorice) as an additive. In drinking water, the guide level of chloride is 25 mg/L (Council Directive 80/778/EC). Chloride is an essential dietary constituent and a dietary inadequacy leads to serious consequence. Chloride is present in biological systems as the main anion in the extracellular space, acting to maintain extracellular volume, and ionic balance. It crosses cell membranes and is involved in the regulation of osmotic pressure, water balance and acid-base balance.

It is sometimes difficult to differentiate the effects of the chloride moiety in chloride salts such as NaCl and KCl from that of the sodium or potassium moiety on physiology and metabolism. Therefore this Opinion should be read in conjunction with the Panel's Opinions on the tolerable upper level of sodium (NDA, 2005a) and potassium (NDA, 2005b).

2. NUTRITIONAL BACKGROUND, FUNCTION, METABOLISM AND INTAKE

2.1 Food levels and dietary intake

Chloride is found in plant and animal based foods in association with monovalent counter cations, mainly sodium and potassium. It is added as salt (NaCl or NaCl/KCl mixtures) to foods during processing, cooking and immediately prior to consumption. The main reasons for the addition of salt during the processing of foods are for taste, texture and preservation.

The chloride content of natural foods varies from around 0.1 to 3 mmol/100g, with fruit containing 0.1 mmol/100g, vegetables, 0.3 mmol/100g and meat fish or eggs 3.0 mmol/100g. The chloride content of processed foods may be much higher; bread 20 mmol/100g; cheese, 30 mmol/100g; salted butter, 40 mmol/100g; and lean raw bacon, 80 mmol/100g.

The assessment of the dietary consumption of chloride in individuals and populations is difficult because of the variable extent to which discretionary additions of salt contribute to the total. The use of dietary assessment methods to determine intake are likely to provide variable underestimates. The most accurate determinations of chloride consumption are derived from measurements of the excretion in urine over 24 hours, although care has to be taken to ensure the completeness of the urine collection (Bingham and Cummings, 1985; Bingham *et al*., 1988).

The main source of chloride in the diet is from salt (NaCl) or (to a lesser extent) salt substitutes (NaCl/KCl mixtures) added during the processing and manufacture of foods (about 70-75% of the total intake) and added to food during cooking and at the table. Naturally occurring chloride in unprocessed foods contributes about 15% of total chloride intake. Discretionary sources of sodium chloride or sodium chloride/potassium chloride mixtures

added during cooking and at table comprise about 10 to 15% of total chloride intake (Sanchez-Castillo *et al.*, 1987). The main sources of chloride from foods in the diet are from cereals and cereal products, particularly bread, and meat and meat products (SACN, 2003). Other sources of chloride are from vegetables.

2.2 Nutritional requirements and recommendations

Chloride is an essential nutrient. The SCF did not establish a Population Reference Intake for chloride but concluded that the requirements should match those for sodium (on a molar basis), i.e. 25 - 150 mmol/day (SCF, 1993). The US Institute of Medicine established an Adequate Intake (AI) for chloride at a level equivalent on a molar basis to that of sodium, since almost all dietary chloride comes with the sodium added during processing or consumption of foods (FNB, 2004). The AI for chloride for younger adults is 2.3 g/day (65 mmol/day), and for older adults and the elderly 2.0 and 1.8 g per day respectively.

For most populations, the habitual levels of chloride consumption greatly exceed the physiological requirements, and there are few data which determine the minimal levels of chloride consumption required to maintain health in people who have adapted to low levels of chloride consumption over long periods of time.

2.3 Function, uptake, distribution and elimination

Dietary chloride is virtually completely absorbed along the length of the intestine. The total body chloride averages about 33 mmol/kg body weight (1.2 g/kg) in a normal adult male (Pike and Brown). Chloride is found in small amounts in a bound form related to connective tissue. Less than 15% of the body's content of chloride is located within cells. The chloride content of blood and the extracellular space is not related to dietary intake but is influenced by intake/plasma concentrations of other electrolytes. The ready transfer of chloride in exchange for bicarbonate between erythrocytes and plasma and in the gastrointestinal tract and renal collecting tubule is an important aspect of the control of blood pH.

The important role played by chloride in the control of electrolyte and acid base equilibria has been well characterised and chloride deficiency is most likely the consequence of an increase in losses, although dietary deficiencies have been described in infants consuming a commercial formula deficient in chloride (Rodriguez-Soriano *et al.*, 1983). Chloride is essential for the formation of hydrochloric acid in the stomach, and hence is involved in the non-specific protection from food borne pathogens. It has generally been considered that chloride readily crosses cell membranes, although the permeability of some smooth muscle, such as vascular smooth muscle, is less than has been assumed. In vascular smooth muscle the active transport of chloride is energetically expensive and appears to be tightly regulated, playing a fundamental role in contraction, an observation of direct relevance to the development of high blood pressure (Chipperfield and Harper, 2000).

Experimental studies have shown that the chloride moiety makes a specific contribution to the effects of sodium chloride on blood pressure, by modulation of renal regulatory systems and plasma renin activity in the rat (Kirchner, 1978; Abboud *et al.*, 1979), dog (Kotchen *et al.*, 1980; Kotchen *et al.*, 1983.), and in the human (Julian *et al.*, 1982; Tomita *et al.*, 1990). There are also specific effects on angiotensin II and aldosterone (Koletsky *et al.*, 1981; Sato *et al.*, 1991; Imig *et al.*, 1993). Dietary loading with sodium chloride leads to positive chloride balance, expanded extracellular volume and increased renal vascular resistance (Passmore *et*

al., 1985; Tomita *et al*., 1990). Chloride is rate limiting for the transport of sodium and chloride in the thin ascending loop of Henle, because of the differences in the affinities of sodium and chloride for the cotransporters. Thus the availability of chloride has a determinant effect on the release of renin (Kotchen *et al*., 1987).

Chloride is lost from the body in sweat (20-80 mmol/day) and other secretions, in stool (5-10 mmol/day) and in urine (1-500 mmol/day).

3. HAZARD IDENTIFICATION

There is evidence that prolonged consumption of excessive chloride as sodium chloride contributes to an elevated blood pressure, which is a risk factor for cardiovascular disease and renal disease (NDA, 2005a). Available evidence indicates that both chloride and sodium contribute to this effect.

In three selective breeds of rats which are especially prone to develop high blood pressure when exposed to dietary salt, chronic selective loading with either sodium or chloride has been found not to induce hypertension (Kotchen *et al*., 1983; Kurtz and Morris, 1983; Whitescarver *et al*., 1984; Kurtz and Morris, 1985; Whitescarver *et al*., 1986; Passmore and Jimenez, 1990; Reddy and Kotchen 1992; Imig *et al*., 1993; Kadota *et al*., 1993; Kunes *et al*., 2004).

Any effects of selective loading with dietary chloride without sodium have been attributed in part to direct effects on acidosis or indirect effects of acidosis on potassium or calcium (Kotchen *et al*., 1988). Boegehold and Kotchen (1989) conclude that the observations indicate that the concomitant provision of a high intake of both sodium and chloride in the diet is required for the expression of experimental salt-sensitive hypertension.

As early as 1929, it was reported that a diet high in sodium bicarbonate did not have the same effect on raising blood pressure as sodium chloride (Berghoff and Geraci, 1929). This has been confirmed by others (Morgan, 1982; Kurt and Morris, 1983; Luft *et al*., 1990). The effect of sodium chloride on blood pressure has not been seen with sodium phosphate (Shore *et al*., 1988), or sodium citrate (Kurtz *et al*., 1987; Tomita *et al*., 1990; Sato *et al*., 1991). Similarly, when the chloride ion is taken without sodium the effects on blood pressure are less evident (Grollman *et al*., 1945; Dole *et al*., 1950). Thus, the findings from human studies support the evidence from animal investigations that both sodium and chloride are required for the effects of salt on blood pressure to be manifest. The evidence would suggest that changes in blood volume underlie these effects (Tomita *et al*., 1990), which are closely related to alterations in the set point for renal salt and water homeostasis. Recent molecular studies implicate a specific role for the anion exchanger pendrin, and its expression in the kidney (Quentin *et al*., 2004).

Adverse changes in heart function and peripheral nerve symptoms associated with high to very high doses of potassium chloride from salt substitutes or supplements (KCl) (4.4-6.2 Cl/day, or more, in addition to diet) have been described, usually in subjects with impaired renal function, but occasionally in healthy adults (NDA, 2005b). These effects are mediated by hyperkalaemia and thus appear to be attributable to potassium intake rather than chloride.

Controlled studies show that gastrointestinal symptoms (ranging in severity from discomfort to mucosal erosion and ulceration) can occur in healthy subjects taking some forms of potassium chloride supplements, e.g. slow release, wax-matrix formulations, with doses ranging from 24 to 120 mmol/day (0.9-4.3 g/day) or more, but incidence and severity seem to be more dependent on the formulation than on dose (NDA, 2005b). It is not possible to distinguish between the possible contributions of chloride and potassium to these effects.

4. DOSE-RESPONSE ASSESSMENT

Higher blood pressure is an acknowledged risk factor for ischaemic heart disease, stroke and renal disease. For groups of individuals there is strong evidence of a dose response relationship between increased consumption of chloride as sodium chloride and higher levels of systolic, diastolic and mean blood pressure (Sacks *et al.*, 2001). The effect of sodium on blood pressure is linked to that of chloride and he adverse effect on blood pressure associated with increasing salt intake appears to be attributable to both sodium and chloride (NDA, 2005a).

Gastrointestinal symptoms (ranging in severity from discomfort to mucosal erosion and ulceration) can occur in healthy subjects taking some forms of potassium chloride supplements, e.g. slow release, wax-matrix formulations, with doses ranging from 24 to 120 mmol/day (0.9 to 4.3 g chloride) or more (NDA, 2005b). The extent to which chloride, as distinct from potassium, contributes to these symptoms is not clear.

CONCLUSIONS AND RECOMMENDATIONS

1. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The available data are not sufficient to establish an upper level for chloride from dietary sources.

2. RISK CHARACTERISATION

The habitual intake of chloride (mainly as sodium chloride) for populations across Europe is high and exceeds the amounts required for normal function. The current levels of chloride consumption as sodium chloride have been associated directly with a greater likelihood of increased blood pressure, which in turn has been directly related to the development of cardiovascular disease and renal disease.

For these reasons, national and international bodies have set targets for a reduction in the sodium chloride consumed in the diet (SACN, 2003; FNB, 2004; WHO, 2003 and 2004).

REFERENCES

Abboud HE, Luke RG, Galla JH, Kotchen TA (1979). Stimulation of renin by acute selective chloride depletion in the rat. Circ Res 44: 815-821.

Berghoff RS and Geraci AS (1929). The influence of sodium chloride on blood pressure. IMJ 56: 395-397.

Bingham SA and Cummings JH (1985). The use of creatinine output as a check on the completeness of 24 h urine collections. Human Nutrition: Clinical Nutrition 39C: 343-353.

Bingham SA, Williams R, Cole TJ, Price CP, Cummings JH (1988). Reference values for analytes of 24 h urine collections known to be complete. Annals of Clinical Biochemistry 25: 610-619.

Boegehold MA and Kotchen TA (1989). Relative contributions of dietary NA+ and Cl- to salt sensitive hypertension. Hypertension 14: 579-583.

Chipperfield AR and Harper AA (2000). Chloride in smooth muscle. Prog Biophys Mol Biol 74: 175-221.

Council Directive 80/778/EEC of 15 July 1980 relating to the quality of water intended for human consumption. Official Journal L 229/11-29.

Dole VP, Dahl LK, Cotzias GC, Eder HA, Krebs ME (1950). Dietary treatment of hypertension; clinical and metabolic studies of patients on the rice-fruit diet. J Clin Invest 29: 1189-1206.

FNB (Food and Nutrition Board) (2004). Dietary Reference Intakes for water, potassium, sodium, chloride and sulfate. Institute of Medicine. National Academy of Sciences.

Grollman A, Harrison TR, Masan MF, Baxter J, Crampton J, Riechman F (1945). Sodium restriction in the diet for hypertension. JAMA 129: 533-537.

Imig JD, Passmore JC, Anderson GL, Jimenez AE (1993). Chloride alters renal blood flow autoregulation in deoxycorticosterone-treated rats. J Lab Clin Med 121: 608-613.

Julian BA, Galla JH, Guthrie GP, Kotchen TA (1982). Renin and aldosterone responses in short-term NaCl or NaHCO3 loading in man. J Lab Clin Med 100: 261-268.

Kadota A, Aoki Y, Ishii N, Numakami K, Ogawa Z, Itoh H, Mitsuta K, Kohno M, Ikenaga H, Saruta T (1993). Effects of sodium and chloride ions on blood pressure in deoxycorticosterone acetate-treated rats. Kitasato Arch Exp Med 65: 65-72.

Kirchner KA, Kotchen TA, Galla JH, Luke RG (1978). Importance of chloride for acute inhibition of renin by sodium chloride. Am J Physiol 235: F444-F450.

Koletsky RJ, Dluhy RG, Cheron RG, Williams GH (1981). Dietary chloride modifies renin release in normal humans. Am J Physiol 241: F361-363.

Kotchen TA, Krzyzaniak KE, Anderson JE, Ernst CB, Galla JH, Luke RG (1980). Inhibition of renin secretion by HCl is related to chloride in both dog and rat. Am J Physiol 239: F44-F49.

Kotchen TA, Luke RG, Ott CE, Galla JH, Whitescarver S (1983). Effect of chloride on renin and blood pressure responses to sodium chloride. Ann Intern Med 98: 817-822.

Kotchen TA, Welch WJ, Lorenz JN, Ott CE (1987). Renal tubular acidosis and renin release. J Lab Clin Med 110: 533-540.

Kotchen TA, Guthrie GP, Boucher LD, Lorenz JN, Ott CE (1988). Dissociation between plasma renin and plasma aldosterone induced by dietary glycine hydrochloride. Am J Physiol 254: E187-E192.

Kunes J, Zicha J, Jelinek J (2004). The role of chloride in deoxycorticosterone hypertension: selective sodium loading by diet or drinking fluid. Physiol Res 32:149-154.

Kurtz TW and Morris RC (1983). Dietary chloride as a determinant of "sodium-dependent" hypertension. Science 222: 1139-1141.

Kurtz TW and Morris RC (1985). Dietary chloride as a determinant of disordered calcium metabolism in salt-dependent hypertension Life Sci 36: 921-929.

Kurtz TW Al-Bander HA, Morris RC (1987). Salt sensitive essential hypertension in men. Is the sodium ion alone important. N Engl J Med 317: 1043-1048.

Luft FC, Zemel MB, Sowers JA, Fineberg NS, Weinberger MH (1990). Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. J Hypertens 8: 663-670.

Morgan TO (1982). The effect of potassium and bicarbonate ions on the rise in blood pressure caused by sodium chloride. Clin Sci 63: 407s-409s.

NDA (Scientific Panel on Dietetic Products, Nutrition and Allergies) (2005a). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Sodium. The EFSA Journal 209, 1-26. http://www.efsa.eu.int/science/nda/nda_opinions/catindex_en.html

NDA (Scientific Panel on Dietetic Products, Nutrition and Allergies) (2005b). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Potassium. The EFSA Journal 193, 1-19. http://www.efsa.eu.int/science/nda/nda_opinions/catindex_en.html

Passmore JC, Whitescarver SA, Ott CE, Kotchen TA (1985). Importance of chloride for deoxycorticosterone acetate-salt hypertension in the rat. Hypertension 7: 115-120.

Passmore JC and Jimenez AE (1990). Separate hemodynamic roles for chloride and sodium in deoxycorticosterone acetate-salt hypertension. Proc Soc Exp Biol Med 194: 283-288.

Pike RL and Brown ML (1984). Nutrition: and integrated approach. 3rd edition. New York, John Wiley & Sons.

Reddy SR and Kotchen TA (1992). Hemodynamic effects of high dietary intakes of sodium or chloride in the Dhal salt-sensitive rat. J Lab Clin Med 120: 476-482.

Rodriguez-Soriano J, Vallo, Castillo G, Oliveros R, Cea JM, Balzategui MJ (1983). Biochemical features of dietary chloride deficiency syndrome: a comparative study of 30 cases. J Pediatr 103: 209-214.

SACN (Scientific Advisory Committee on Nutrition) (2003). Salt and Health. London, The Stationery Office.

Sanchez-Castillo CP, Warrender S, Whitehead TP, James WP (1987). An assessment of the sources of dietary salt in the British population. Clin Sci 72: 95-102.

Sato Y, Ogata E, Fujita T (1991). Role of chloride in angiotensin II induced salt-sensitive hypertension. Hypertension 18: 622-629.

SCF (Scientific Committee on Food) (1993). Reports of the Scientific Committee on Food (31st series). Commission of the European Community, Luxembourg, pp. 177-189.

Shore AC, Markander ND, MacGregor GA (1988). Randomized crossover study to compare the blood pressure response to sodium loading with and without chloride in patients with essential hypertension. J Hypertens 6: 613-617.

Tomita Y, Ueno M, Tsuchihashi T, Muratani H, Kobayashi K, Takishita S, Fujishima M (1990). Chloride ion plays an important role in sodium induced volume expansion in normal humans. Am J Hypertens 3: 485-487.

Quentin F, Chambrey R, Trinh-Trang-Tan MM, Fysekidis M, Cambillau M, Paillard M, Aronson PS, Eladari D (2004). The Cl^-/HCO_3^- exchanger pendrin in the rat kidney is regulated in response to chronic alterations in chloride balance. Am J Physiol 287: F1179-F1188.

Whitescarver SA, Ott CE, Jackson BA, Guthrie GP, Kotchen TA (1984). Saltsensitive hypertension: contribution of chloride. Science 223: 1430-1432.

Whitescarver SA, Hotlzclaw BJ, Downs JH, Ott CE, Sowers JR, Kotchen TA (1986). Effect of dietary chloride on salt-sensitive and renin-dependent hypertension. Hypertension 8: 56-61.

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