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

(REQUEST N° EFSA-Q-2003-018)
(ADOPTED ON 21 APRIL 2005)

SUMMARY

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

Sodium 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) during processing, cooking and immediately prior to consumption, but also in other forms, for example as sodium nitrate, sodium phosphate or sodium glutamate. The main reasons for the addition of salt during the processing of foods are for flavour, texture and preservation.

Mean daily sodium intakes of populations in Europe range from about 3-5 g (about 8-11g salt) and are well in excess of dietary needs (about 1.5 g sodium/day in adults). The main source of sodium in the diet is from processed foods (about 70-75% of the total intake), with about 10-15% from naturally occurring sodium in unprocessed foods and about 10-15% from discretionary sodium added during cooking and at the table.

The major adverse effect of increased sodium intake 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. The effect of sodium on blood pressure is linked to that of chloride. For groups of individuals there is strong evidence of a dose dependent rise in blood pressure with increased consumption of sodium as sodium chloride. This is a continuous relationship which embraces the levels of sodium habitually consumed and it is not possible to determine a threshold level of habitual sodium consumption below which there is unlikely to be any adverse effect on blood pressure.

While blood pressure, on average, rises with increased sodium intake, there is well-recognised variation between individuals in the blood pressure response to changes in sodium chloride intake. Individuals with hypertension, diabetes, and chronic kidney disease, as well as older-age persons, tend to be more sensitive to the blood pressure raising effects of sodium intake. The blood pressure response to sodium can be modulated by a range of factors which include other components of the diet (e.g. potassium), relative body weight, and level of physical activity, as well as fixed factors which include age, gender and genetic factors.

Epidemiological studies indicate an association of increased risk of morbidity and mortality from cardiovascular diseases, including coronary heart disease and stroke, with increasing sodium intake. Evidence that high sodium intake may have a direct adverse effect on heart function, independent of any secondary effect due to changes in blood pressure, is not conclusive. Sodium is not carcinogenic but high intakes 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 upper level (UL) for sodium from dietary sources.

There is strong evidence that the current levels of sodium consumption 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 sodium consumed in the diet.

KEY WORDS

Sodium, blood pressure, stroke, cardiovascular disease, 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.

ASSESSMENT

1. INTRODUCTION

Sodium (Na) is a metal with an atomic mass of 23. It is found widely in nature and as a normal constituent of foods. It is added to foods, most frequently as sodium chloride (NaCl), common known as salt (1 mmol is equivalent to 23 mg sodium and approximates 58 mg sodium chloride), but also as other salts, e.g. nitrate, nitrite, phosphates, glutamate. In drinking water, the guide level of sodium is 20 mg/L (Council Directive 80/778/EEC). Sodium is an essential nutrient and a dietary inadequacy may lead to serious consequences. Sodium is present in biological systems as the main cation in the extracellular space, acting to maintain extracellular volume and plasma osmolality.

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

2. NUTRITIONAL BACKGROUND, FUNCTION, METABOLISM AND INTAKE

2.1. Food levels and dietary intake

Sodium is found in plant and animal based food and also in drinking water. Sodium is added to foods, commonly as sodium chloride, during processing, cooking and immediately prior to consumption, but also in other forms, for example as sodium nitrate, sodium phosphate or sodium glutamate. The main reasons for the addition of salt during the processing of foods are for flavour, texture and preservation.

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.

The sodium 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 content of sodium as sodium chloride in 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. It is difficult to obtain reliable information on the sodium chloride content of foods as consumed, because of variable practices in terms of processing, food preparation and personal preferences.

The assessment of the dietary consumption of sodium 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 of the true intake, which has been assessed as around 20% for some populations. The most accurate determinations of sodium consumption are derived from measurements of the excretion of sodium 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 amount of sodium consumed, varies widely between populations, within populations, and within individuals with time. The Intersalt study was a study from 52 centres in 32 countries around the world, in which 24 hour specimens of urine were collected from 10,079 men and women aged 20-59 years of age (Intersalt Cooperative Research Group, 1988). There were 20 centres from 12 countries in Western Europe who participated, providing data from 3,942 men and women. In this group the median sodium excretion varied from 135 to 180 mmol/24 hours (equivalent to 3.1-4.1 g Na or 7.9-10.5 g NaCl) (Perry and Beevers, 1992). Estimates of the intake of sodium as sodium chloride were 8-9 g in Belgium, Denmark and The Netherlands and 9-11 g in Finland, Italy, Portugal, Spain and the UK. For Romania, the daily consumption of sodium as sodium chloride has been estimated to be 14 g/person (WHO, 2004). Although there are suggestions that manufacturers have attempted to reduce the sodium chloride content of some products, such as bread, the amount of sodium consumed in the UK did not change between 1987 (sodium excretion in urine for men 173 mmol/day, and for women 132 mmol/day) and 2001 (sodium excretion in urine for men 187 mmol/day, and for women 139 mmol/day), based on the measured excretion of sodium in urine in nationally representative samples (Gregory *et al*, 1990; Henderson *et al*, 2003). Data from the UK suggest that average daily intake of sodium in children aged 4-6 years and 7-10 years exceeds 5 g and 6 g, respectively (SACN, 2003). This compares with the average intake of sodium assessed for a group of children in the Dortmund Nutritional and Anthropometrical Longitudinally Designed Study of 751 children from 3 months to 18 years of age, where consumption was about 3g/day at age 4 to 6 years, and 4.5 g/day at 10 to 12 years, but these values exclude any discretionary sodium chloride added in the home (Alexy and Kersting, 1999).

The main source of sodium in the diet is from processed foods, and it is estimated that this non-discretionary consumption comprises about 70-75% of the total intake in most European countries. Naturally occurring sodium in unprocessed foods contributes about 10 to 15% of total sodium intake. Discretionary sources of sodium added during cooking and at the table comprise about 10 to 15% of total intake (Sanchez-Castillo *et al*, 1987).

Based on the National Diet and Food Survey in the UK, cereals and cereal products (particularly bread) were estimated to contribute 35% of total sodium consumption, or about 2.3 g/day, with 1.7 g/day coming from meat and meat products (particularly processed meats) to contribute 26% to the total. Vegetables contribute to 7%, milk and milk products, 8%, fats spreads, 3% and cheese, 4% made lesser contributions (NDNS, 2003), but individual composite foods or savoury snacks can be especially high in sodium.

2.2. Nutritional requirements and recommendations

Human populations survive on wide extremes of habitual sodium consumption from 10 to 450 mmol/day. The ability to survive at low levels of consumption is dependent upon adaptive mechanisms which reduced losses in sweat, stool and urine. For most populations, the habitual levels of sodium consumption greatly exceed the physiological requirements, and there are few data which determine the minimal levels of sodium consumption required to maintain health in people who have adapted to low levels of sodium consumption over long periods of time (Allsopp *et al*, 1998). As the metabolism of sodium is closely related to that of water and other nutrients, the need for sodium can only be adequately assessed when the provision of water and all other nutrients is adequate.

For sodium, the acceptable range of intakes for adults established by the Scientific Committee on Food was 25 to 150 mmol/day (SCF, 1993). This compares with the Adequate Intake identified in the USA as

65 mmol/day for adults up to 50 years of age, 55 mmol/day for those between 51 and 70 years of age, and 50 mmol/day for those aged over 70 years of age (FNB, 2004). The Reference Nutrient Intake was set at 70 mmol/day for the UK (Department of Health, 1991).

2.3. Function, uptake, distribution, and elimination

Dietary sodium is virtually completely absorbed along the length of the intestine and the active transport of sodium is closely linked to the wider ability of the small intestine to absorb other nutrients.

Sodium is the major extracellular cation in the body, and the total body content is tightly regulated. The normal adult contains around 5600 mmol sodium (129 g Na). About half of this, 2800 mmol, is dissolved in the extracellular fluid, with 300 mmol in the intracellular compartment. In healthy adults, the total exchangeable sodium is about 40-50 mmol/kg body weight. Bone contains about 2500 mmol of sodium, part of which is exchangeable with isotopically labelled sodium, and the remainder is deeper and less accessible as an intrinsic part of the crystal lattice of bone (Ganong, 1983).

Sodium is the main osmolyte in the extracellular fluid, maintained within a narrow range at a concentration of 135-145 mmol/L and therefore plays a fundamental role in maintaining extracellular fluid volume and together with potassium in maintaining total body water homeostasis. It contributes to the establishment of the membrane potential of most cells and plays a direct role in the action potential required for the transmission of nerve impulses and muscle contraction. The active absorption of sodium from the lumen of the gastrointestinal tract is important in the absorption of nutrients.

The regulation of total body content is closely related to the regulation of total body potassium, the main intracellular cation, and the regulation of total body water. The membrane bound sodium-potassium pump (the sodium-potassium-activated adenosine triphosphate Na+-K+ ATPase) plays a fundamental role in maintaining the partitioning of sodium and potassium between the extracellular and intracellular compartments respectively, and the energy required for this process represents a significant component of the metabolic rate.

Sodium 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). Under normal conditions, gastrointestinal and cutaneous losses are minimal and the maintenance of the total body content of sodium is predominantly a characteristic of the regulation of renal excretion. Sodium is actively conserved in the body, with the kidneys playing a major role. Approximately 18 mmol of sodium are filtered per minute and over 99% is actively reabsorbed. Sodium depletion is seldom a consequence of a deficient intake, and more usually the result of excessive losses through excessive sweating or gastrointestinal losses. Sodium depletion may be manifest as low blood pressure and muscle cramps. Excessive sodium leads to an increase in plasma osmolality, resulting in the sensation of thirst, and an increase in the secretion of antidiuretic hormone which increases water retention in the kidney.

The excretion of sodium in urine is highly regulated, through the complex interaction of hormonal, nervous and other systems which enable tight homeostatic control. In this way urinary sodium excretion can be adjusted over a very wide range to achieve sodium balance, from virtually zero when sodium needs to be retained in the body, to 1,100 mmol/day when intake is high (Roos *et al*, 1985). The regulatory systems are highly efficient and include resetting of glomerular filtration rate, the reabsorption of sodium in the proximal and distal tubule under neurohumoral control, adapting in both the short and the longer term to variation in intake and status. Following a change in diet sodium balance may be restored in 5 to 7 days, as sodium excretion comes into equilibrium with intake. The period taken to restore balance is variable amongst individuals and takes longer in some people, especially at the extremes of age, in young infants and older people (Ganong, 1983; Pecker and Laragh, 1991). These mechanisms are responsive to changes in total body water and extracellular fluid volume, to the function and integrity of cells in general and specialised cells in different locations, to ensure the effective delivery of blood to all tissues, including the brain.

3. HAZARD IDENTIFICATION

3.1. Animal toxicity data

For sodium chloride, the oral LD_{50} in rats is 3000 mg/kg and in mice is 4000 mg/kg (EGVM, 2003; RTECS, 1998).

3.1.1. Carcinogenicity

Evidence from studies in laboratory animals indicates that high intakes of salt may increase the susceptibility to various carcinogens and the incidence of gastric cancer, but that salt is not of itself carcinogenic (Cohen and Roe, 1997). The possible biological pathways by which salt increases cancer of the stomach have been well articulated, although salt itself is not considered intrinsically carcinogenic, intake of higher concentrations of salt leads to damage to the protective mucin and the mucosal layer of the stomach, which leads to an inflammatory regenerative response with increased DNA synthesis and cell proliferation. These effects have been considered to be more closely related to local effects where high concentrations are achieved, which physically damage cells, rather than any direct effect in damaging DNA (Cohen and Rose, 1997). By contrast specific highly salted foods have been shown to enhance chemically induced carcinogenesis in the glandular stomach of rats (Takahashi *et al*, 1983 and 1994). Quite apart from the high salt content, these foods also contain many other compounds which might increase the risk of cancer (IARC, 1993). The consumption of salt is thought to create an increased susceptibility, which typically enhances carcinogenesis induced by other specific carcinogens, such as nitrosamines (Watanabe *et al*, 1992; Takahshi *et al*, 1994; Furihata *et al*, 1996; Iishi *et al*, 1999; Cohen and Roe, 1997; IARC, 1990).

Infection with *Helicobacter pylori* has been considered to be an important aetiological factor in the development of gastric cancer (IARC, 1994). Mongolian gerbils were treated with 20 ppm of N-methyl-N-nitrosourea (MNU) in their drinking water alternate weeks for 5 weeks. At 11 weeks the animals were inoculated with *H. pylori*, and after 12 weeks the animals were fed a 10% high salt diet. A high salt diet enhanced the effects of *H. pylori* infection on gastric carcinogenesis, and these two factors acted synergistically to promote the development of stomach cancer. *H. pylori* promoted stomach cancer more than the high salt diet (Tatematsu, 2003). Big Blue transgenic mice were inoculated with *H. pylori* and developed severe gastritis, and after 12 months they exhibited mutagenic effects. There was no added effect of a high salt diet (Touati *et al*, 2003).

3.1.2. Genotoxicity

Studies carried out *in vitro*, have shown that when cells are exposed to high concentrations of sodium chloride, there are physical effects which can lead to direct damage to chromosomes or to DNA which are non-specific in nature.

3.1.3. Reproductive toxicity

In rats fed experimental diets from one week prior to conception and throughout gestation, the proportion of male pups was lower as the sodium chloride content of the diets increased from 0.8 to 4%. No differences were observed in litter sizes or general health of the offspring (Bird and Contreras, 1986).

Dams were maintained on diets which contained 0.12, 1.0, and 3.0% sodium chloride throughout pregnancy, and the offspring were given the same diets until day 30 of life, followed by a diet containing 1.0% sodium chloride (Contreras and Kosten, 1983). Preference tests for solutions of sodium chloride, potassium chloride or glucose were carried out at 90 days of age. Preferences were non-specific. Although those raised on a high salt diet showed an elevated preference for sodium chloride solutions, males also showed a preference for glucose solutions. The weights of adrenal glands of the males in the highest salt group were significantly lower than controls.

Borderline hypertensive rats fed a diet containing 8% sodium chloride from conception to weaning: offspring demonstrated higher blood pressure as adults (Hunt and Tucker, 1993).

Pregnant Brattleboro rats fed 8.5% sodium chloride in the diet showed a higher concentration of sodium chloride in amniotic fluid, and supplementation of pups with sodium post weaning led to an elevation of arterial blood pressure (Hazon *et al*, 1988).

3.1.4. Cardiovascular health and blood pressure

There is a large body of data on rodent models which indicate that depending on genetic strain there may be different degrees of sensitivity to dietary sodium. The immediate relevance of this work for long term human health is not clear (Swales, 1994).

Perhaps the most informative intervention study of relevance to human physiology is that conducted by Denton *et al* (1995) on the effect of increased levels of sodium chloride on the blood pressure of chimpanzees. A colony of 26 chimpanzees, aged 5 to 18 years, was maintained on a vegetable and fruit

diet, very low in sodium and high in potassium. Sodium chloride in the range habitually consumed by human populations was added to the diet of one half of the animals over a period of 20 months. The stepwise addition of sodium chloride caused a highly significant, stepwise rise in systolic and diastolic blood pressure. No threshold effect was observed. The increase in blood pressure reversed completely following the cessation of the added sodium chloride to the diet. The effect was variable amongst different animals, with some having a larger and others a smaller or no rise in blood pressure.

3.2. Human toxicity

3.2.1. Acute effects

The acute ingestion of 0.5 to 1 g sodium chloride per kg body weight can be toxic to fatal to most people. There are local effects within the gastrointestinal tract leading to ulceration. There may be direct or secondary systemic metabolic perturbations in fluid and acid base balance. There is neurological dysfunction leading to seizures and damage to the central nervous system, muscle dysfunction and renal damage.

3.2.2. Chronic effects

3.2.2.1. Carcinogenicity

The evidence for an effect of NaCl on the incidence of cancer is less clear in humans than in experimental animals. The data have been recently reviewed by the World Cancer Research Fund (WCRF, 1997) and the Institute of Medicine (FNB, 2004). Salt consumption has been associated with cancer of the naso-pharynx and cancer of the stomach. An increased risk of cancer of the larynx, mouth and pharynx has been associated with consumption of salt-preserved meat and fish (Zheng *et al*, 1992; Anderson *et al*, 1978). Eight case control studies of people from China living in different parts of the world found statistically significant increases in risk for nasopharyngeal cancer, with odds ratio varying from 2.1 to 37.7, and suggesting that childhood exposure was particularly important (WCRF, 1997). Experimental studies in rats and hamsters corroborate the findings, and consideration of aetiological factors indicates that volatile carcinogenic nitrosamines might be particularly important. In areas where mortality from nasopharyngeal carcinoma was particularly high, there were highly significant correlations with total volatile nitrosamines in salted fish samples. There is some evidence to suggest a possible interaction with Epstein-Barr virus, which appears to be activated by the chemicals found in salted fish (Ho *et al*, 1976; Shao *et al*, 1988).

The main body of evidence relates to cancer of the stomach. Throughout the world, a strong and consistent relationship has been found between the intake of salt and salted foods and the incidence of cancer and pre-cancerous lesions of the stomach. Biological pathways by which salt increases cancer of the stomach are best explained by salt in the diet acting to damage the protective mucosal layer of the stomach, thereby enhancing carcinogenesis. Thus, although salt is not considered to be intrinsically carcinogenic, a high intake of salt leads to damage of the protective mucosal layer of the stomach, and results in an inflammatory regenerative response, increased DNA synthesis and cell proliferation. Prolonged damage results in chronic atrophic gastritis. Over time these changes provide favourable conditions for mutations to occur, and typically enhance carcinogenesis induced by specific carcinogens (Sugimura, 2000). There is a significant relationship between infection of the stomach with *H. pylori* and cancer of the stomach, and it is suggested that this is a consequence of the bacterial infection acting as a co-factor with salt on a damaged gastric epithelium (Joossens *et al*, 1996; Tsugane, 2005).

3.2.2.1.1. Ecological study

Based on the data collected in the Intersalt study, a comparison has been made to explore the possibility that high urinary excretion of sodium and/or high nitrate might be considered as risk factors for stomach cancer in 39 populations from 24 countries, based on sodium excretion in 24 hour urine specimens for 5756 people. The data were age and sex standardised between 20-49 years and the Pearson correlation for stomach cancer was 0.70 in men and 0.74 in women. The analysis indicated that the importance of nitrate as a risk factor for stomach cancer mortality increased markedly with higher sodium levels. The relationship of stomach cancer mortality with sodium was stronger than with nitrate and the authors conclude that salt intake is likely the rate limiting factor for stomach cancer mortality at the population level (Joossens *et al*, 1996). There was no increase noted in the incidence of cancer mortality for men with sodium intakes less than 117 mmol (2.7 g sodium) per day, and for women with sodium intakes less than 91 mmol (2.1 g) per day.

3.2.2.1.2. Cross-sectional studies

A significant positive association has been observed between salt/sodium intake and risk of gastric cancer in most, but not all, of the cross sectional studies (WCRF, 1997; FNB, 2004). More recent evidence suggests that the risk might be greatest in individuals with specific genotypes (Chen *et al*, 2004). In an area of Taiwan where there is a high mortality for stomach cancer, a survey to determine risk factors was carried out in 312 subjects (174 men and 138 women) in 1995. The presence of intestinal metaplasia was determined using gastro-endoscopic examination. The consumption of salted foods was associated with an increased risk of intestinal metaplasia, with an odd-ratio (OR) 2-3. The risk appeared to be greatest among subjects with specific genotypes: GSTMI null, GSTTI non-null and CYP2EI cl/cl.

3.2.2.1.3. Case-control studies

WCRF (1997) reported that of sixteen case control studies, eight estimated overall dietary salt or sodium intake, and of these four have shown strong statistical increase in risk, with four showing no substantial association. The relative risk for gastric cancer, associated with higher intakes of salt, has varied from 1.4 to 6.7 (FNB, 2004). In a hospital-based case control study carried out in Korea, 69 patients newly diagnosed as early gastric cancer were compared with 199 healthy subjects. There was *H. pylori* seropositivity in 88% cases and 75% controls (OR=5.3). Adaptive salt concentration was significantly and positively associated with early gastric cancer risk ($p<0.01$). Subjects seropositive for *H. pylori*, and a high salt preference had 10-fold higher risk of early gastric cancer than those without *H. pylori* infection and low salt preference (p for interaction 0.047) (Lee *et al*, 2003).

3.2.2.1.4. Prospective studies

In two prospective studies, salt intake was significantly and directly associated with gastric cancer in dose response fashion in men but not in women.

A cohort study was carried out in The Netherlands of 120,852 men and women aged 55-69 years at baseline in 1986. The exposure to salt was determined using a diet questionnaire. After 6.3 years of follow up, 282 incident cases of cancer were available for analysis, with 3123 sub-cohort members. In multivariate analyses adjusted for age, sex, smoking, education, stomach disorders, history of stomach cancer in the family, rate ratios for increasing quintiles of energy adjusted intake of dietary salt were not significant. An inverse trend was found between stomach cancer and salt added at the hot meal (p for trend 0.04). Positive associations were found for bacon (relative risk [RR] 1.3), and other sliced cold meats (RR 1.29). Separate analyses among subjects with self-reported stomach disorders revealed higher RR of stomach cancer for dietary salt and types of cured meat. It was concluded that the intake of dietary salt and several types of cured meat were weakly positively associated with stomach cancer risk (van den Brandt *et al*, 2003).

A population-based prospective study was carried out in Japan, where the majority of men had been infected with *H. pylori*. A total of 18,684 men and 20,381 women aged 40-59 years completed a food frequency questionnaire and were followed from 1990 to 2001. A total of 486 cases, 358 men and 128 women were documented with gastric cancer confirmed by histology. The quintile category of salt intake was associated with gastric cancer in a dose dependent fashion for men (p for trend <0.001; median g/day, 2.9, 4.8, 6.1, 7.5, 9.9), while there was no clear trend identified for women (p for trend 0.48; median g/day 2.6, 4.2, 5.3, 6.4, 8.2). In men there was no obvious break point below which the risk was reduced (Tsugane *et al*, 2004).

3.2.2.2. Bone health

In surveys of free living individuals and in physiological studies where dietary loads of sodium chloride have been administered, there is consistent evidence that increased sodium ingestion induces a substantial increase in the urinary excretion of calcium (SACN, 2003; FNB, 2004; New and Bonjour, 2003). On this basis, it has been hypothesised that higher levels of sodium ingestion might compromise bone health. The available evidence suggests that sodium-induced increase in urinary calcium excretion leads to an increased calcium absorption by the gastrointestinal tract, mediated via parathyroid hormone (Cashman and Flynn, 2003). However, this adaptive mechanism may be insufficient to prevent an increase in bone resorption in some individuals, e.g. postmenopausal women with a particular vitamin D receptor genotype (Harrington *et al*, 2004). Whether this increase in bone resorption leads to net bone loss is unclear and thus the evidence for a direct effect of sodium ingestion on bone health is not conclusive.

3.2.2.3. Cardiovascular function

Systematic reviews of the evidence which relates consumption of sodium in the diet with cardiovascular health have been reported recently (SACN, 2003; FNB, 2004).

3.2.2.3.1. Heart

An increase in the mass of the left ventricle of the heart is a powerful predictor of cardiovascular morbidity and mortality, including myocardial infarction, stroke, congestive heart failure and sudden death (Bikkina *et al*, 1994; Casale *et al*, 1986; Koren *et al*, 1991; Levy *et al*, 1990). In the Framingham study, elevated left ventricular mass as measured by echocardiography was associated with an increased incidence of cardiovascular disease after adjustment for traditional risk factors (Levy *et al*, 1990). For people with left ventricular hypertrophy, the 5-year mortality was 33% men and 21% for women (Koren *et al*, 1991).

An increase in the mass of the left ventricle might be the consequence of high blood pressure, but there is evidence that a high sodium intake might have direct effect on heart leading to an increase in left ventricular mass. In most studies, the association between urinary sodium and left ventricular mass persists after adjustments for other determinants of left ventricular mass, such as blood pressure (du Cailar *et al*, 2002; Liebson *et al*, 1993).

In a cross sectional study of 42 patients with essential hypertension Schmieder *et al* (1988), using stepwise multiple linear regression analysis, found that sodium excretion was the strongest predictor for left ventricular posterior wall thickness independently of other variables (sodium excretion correlated with ventricular posterior wall thickness, $r=0.64$, $p< 0.001$, and septal wall thickness, $r=0.78$). Sodium excretion varied from 37 to 356 mmol/day. No break point was identified in the relationship. Alderman *et al* (1995) carried out a cross-sectional analysis of 1900 men and 1037 women and concluded that there was a non-significant relationship between urinary sodium and left ventricular hypertrophy assessed by electrocardiography. Du Cailar *et al* (2002) in a cross-sectional study of 839 men and women, using multivariate analysis, found a strong relationship between sodium excretion and left ventricular mass in men and women. Liebson *et al* (1993 and 1995) examined the effect of different therapeutic interventions on left ventricular mass in a randomized double blind trial of 902 people with mild essential hypertension. There were significant changes in left ventricular mass determined by echocardiography from 3 months and maintained to the end of the study period at 48 months. The authors concluded that sodium reduction was effective in reducing left ventricular mass, which was greater than could be accounted for by a change in blood pressure, leading to the conclusion that sodium reduction might be more effective in improving left ventricular mass than in reducing blood pressure, although an effect of weight loss could not be excluded.

These studies raise the possibility that sodium has a direct adverse effect on left ventricular structure and function, independent of any secondary effect due to changes in blood pressure. Recent evidence suggests that the primary mediator of the effects of salty diets on the left ventricle might be marinobufagenin. Marinobufagenin is produced endogenously in response to high levels of sodium chloride consumption. It is an ouabain-like compound which has a specific effect on the alpha-1 isoform of the sodium-potassium pump in the coronary microvasculature, which is suggested might lead to altered ventricular structure and function (Manunta and Ferrandi, 2004; McCarty, 2004).

3.2.2.3.2. Blood vessels

There is experimental evidence that a high sodium diet results in dilatation and reduced distensibility of arteries. Consumption of a higher sodium diet, leading to an increase in plasma sodium, may be sufficient to stimulate vascular reactivity (Simon and Kocks, 2003). Thus increased sodium consumption may exert a direct effect on the rigidity of vessels and also on their responsiveness to vasodilatory stimuli (Kocks *et al*, 2004). In untreated, older hypertensives, 4 weeks of sodium restriction increased compliance of the carotid artery significantly by 27% (Gates *et al*, 2004).

3.2.2.3.3. Blood pressure

Usual blood pressure is strongly and directly related to overall mortality and to mortality from stroke, ischaemic heart disease, and other vascular mortality, without any evidence of threshold, down to blood pressures of at least 115mm Hg (systolic) and 75 mm Hg (diastolic) (Prospective Studies Collaboration, 2002). Thus, the risk is increased even within what is considered to be a normal range for blood pressure (less than 140/90 mmHg in adults, WHO, 1996). Analysis of the burden of ill-health and disease which can be attributed to different risk factors indicates that a considerable proportion of

cardiovascular disease is related to non-optimal blood pressure, translating to deaths and years of life lost to death and disability (Lawes *et al*, 2004).

Blood pressure tracks throughout life, and therefore a higher blood pressure at an earlier age is more likely to be associated with a higher blood pressure in later life. It has been suggested that the salt content of the diet during early life might have an important determinant effect on the likelihood of higher blood pressure in adulthood. The longer term effects may be related to the acquisition of a preferential taste for salt, but there is also evidence that it reflects a change in the ability of the individual to handle salt. Salt sensitivity is the term used to identify those individuals in whom the acute ingestion of salt leads to identifiable metabolic changes, either an alteration in blood pressure, or a constraint on the renal ability to respond to a salt load (SACN, 2003; FNB, 2004). There is some evidence of a genetic predisposition to salt sensitivity, as the prevalence is higher in some racial groups, for example African-Americans. The increased susceptibility to the adverse effect of sodium on blood pressure with ageing is thought to reflect a declining renal capacity to handle salt with the decline in the number of nephrons and their function with time.

Although much of the effect on blood pressure has been attributed to the sodium moiety, there is a body of evidence which indicates that the chloride ion also has a role to play in a predisposition to salt-sensitive hypertension (Boegehold and Kotchen, 1989). 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).

The impact of dietary sodium (salt) on blood pressure may be affected by consumption of potassium or calcium. The urine sodium-potassium ratio is a stronger correlate of blood pressure than sodium or potassium alone (Intersalt study, 1988; Kwah and Barrett-Conner, 1988; Mc Carron *et al*, 1984). Oral potassium supplementation lowered blood pressure and the magnitude of this effect was found to be more pronounced in subjects consuming a diet high in salt (Cappuccio and Mc Gregor, 1991).

3.2.2.3.3.1. Infants and children

There is evidence that blood pressure during early life might be related to the concurrent consumption of sodium, and that the level of sodium consumption during early life might have longer term effects on blood pressure.

Pomeranz *et al* (2002) compared the effect on blood pressure in term infants of consuming human milk (sodium content 7 mmol/L), or consuming a formula with a low content (sodium 9.5 mmol/L), or a higher sodium content (16.6 mmol/L), during the first 8 weeks of life. Compared with infants consuming human milk, systolic blood pressure was significantly increased in infants fed a formula with the higher sodium content at 8 weeks of age. Even following reversion to a lower sodium intake, this group of infants had higher blood pressure than the breast fed infants at 24 weeks of age.

Hofman *et al* (1980) carried out an observational study of the relationship between blood pressure and the sodium content of drinking water in 348 children aged 7.7 to 11.7 years of age in The Netherlands and demonstrated a relationship between sodium consumption and blood pressure in the short term. They went on to recruit 476 healthy newborns in a single centre during 1980 who were randomized to receive either a low (4.9 mmol/day) or a high sodium diet (13.9 mmol/day), with measurements of blood pressure being taken every 4 weeks. After 25 weeks of intervention systolic blood pressure was 2.1 mm Hg lower in the low sodium group than in the high sodium group, after adjustment for weight and length at birth and systolic blood pressure in the first week of life (Hofman *et al*, 1983). Longer term follow-up was carried out after 15 years in 35% of the original cohort, and the adjusted systolic blood pressure was 3.3 mm Hg lower in the children who had been assigned to the low sodium group during infancy (Geleijnse *et al*, 1996). A cohort of 233 children aged from 5 to 17 years from The Netherlands were followed for 7 years with annual measurements of sodium excretion based on timed overnight specimens. Mean

systolic blood pressure increased with age, but this change was lower when the sodium intake relative to potassium intake was lower and when the intake of potassium was higher (Geleijnse *et al*, 1990).

An intervention study was carried out to determine the effect of reducing sodium intake in 80 children aged 6 to 9 years who had high blood pressure. Sodium consumption was determined from diet diaries and overnight urine collections. One year after randomisation sodium intake was significantly lower in the intervention group, 87 compared with 130 mmol/24 hours, but no significant differences in blood pressure were recorded (Gillum *et al*, 1981).

Cooper *et al* (1980) measured urinary sodium in seven consecutive 24 hour urine collections from 73 children aged between 11 and 14 years. They demonstrated a significant correlation between mean individual sodium excretion and blood pressure, which persisted when they controlled for height, weight, pulse, age, sex and race, but was eliminated when they controlled for creatinine excretion. They were not able to reproduce these findings in later studies carried out according to the same protocol (Cooper *et al*, 1983).

Complete collections of urine and ambulatory blood pressure over 24 hours were determined in 85 obese and 88 non-obese children aged 3 to 19 years. Weight and sodium excretion were directly associated with systolic blood pressure, but the relationship was modified in obese children compared with controls (Lurbe *et al*, 2000).

3.2.2.3.3.2. Adults

Observational and ecological studies show that across populations there is a strong direct relationship between average intakes of salt and prevalence of hypertension (Dahl, 1960; Gleiberman, 1973; Elliott, 1991). The results are less consistent for studies within populations, which often lack sufficient statistical power, or variation in habitual levels of salt consumption (FNB, 2004).

Systematic reviews

A number of systematic reviews have been carried out to characterise the literature on the relationship between dietary sodium consumption and blood pressure. Adherence to a diet low in sodium over long periods of time is difficult to achieve, because salt is so widely distributed throughout different foods (Kumanyika *et al*, 2005). In reviewing the effect of dietary salt on blood pressure, the Institute of Medicine (FNB, 2004) assessed studies of shorter and longer duration separately, to take some account of these difficulties in compliance, and also the possibility of time-related differences in biological responses. Although on average a reduction in the sodium intake appears to lower blood pressure, the individual response may be highly variable, either because of methodological difficulties related to measurement, or to genuine biological variability (Miller *et al*, 1987).

A number of reviews have included studies with a duration of observation of less than 6 months (Law *et al*, 1991 a and b; Midgley *et al*, 1996; Cutler *et al*, 1997; Graudal *et al*, 1998; Alam and Johnson, 1999). For example, the objective for Midgley *et al* (1996) was to determine whether restriction of dietary sodium lowers blood pressure in hypertensive and normotensive individuals. Fifty-six trials met inclusion criteria. Publication bias was evident. Studies were included which used urinary sodium as a proxy measure of dietary sodium intake. The age of the normotensive participants was 26 years, and for the hypertensive subjects 47 years. The median urinary sodium in the hypertensive group was 158 mmol/day, and in the normotensive group 164 mmol/day and the average change in sodium consumption in the hypertensive group was 95 mmol/day, and in the normotensive group 125 mmol/day. Following adjustment for measurement error, the decrease in blood pressure for a 100 mmol/day reduction in daily sodium excretion was 3.7 mm Hg systolic and 0.9 mm Hg diastolic in the hypertensive, and 1.0 mm Hg systolic and 0.1 mm Hg diastolic in the normotensive trials, respectively. There was wide variability in response between studies. The decreases were greater in individuals who were older and in those who had hypertension. Trials of shorter duration tended to show greater decreases in blood pressure. This raises the question of the extent to which variability in response may be related to the degree of compliance. There were no changes in urinary potassium or in body weight where these had been measured.

The studies included in more recent systematic reviews have sought to include studies in which the period of observation extends for longer than 6 months (Ebrahim and Smith, 1998; Hooper *et al*, 2002). In general the longer studies provide an insight into the ability of individuals to adhere to advice to consume a diet low in salt, as much as the effect of a lower salt diet on outcomes. Hooper *et al* (2002) were able to identify three trials in people with hypertension (n=2326); five in people with untreated

hypertension (n=387); three in people with treated hypertension (n=801). They had been followed up for periods from 6 months to 7 years and the endpoints were mortality and cardiovascular events. There were reductions in both systolic and diastolic blood pressure at both intermediate and late follow up, and reductions in urinary sodium excretion at both intermediate and late follow up. The low salt diets seemed to allow people with hypertension to stop taking medication. In eleven long-term randomised controlled trials of dietary salt reduction there were few data on mortality from cardiovascular events or quality of life but they did show significant falls in systolic blood pressure and urinary sodium excretion 13 to 60 months after initial advice. In their review, He and MacGregor (2004) included 734 subjects from 17 trials of individuals with high blood pressure and 2220 individuals with normal blood pressure from 11 trials. For individuals with normal blood pressure there was a reduction in urinary sodium of 74 mmol/24 hours (4.4 g salt/day) and a fall in systolic blood pressure of 2.03 mmHg, and a fall in diastolic blood pressure of 0.99 mmHg. For those with elevated blood pressure there was a reduction in urinary sodium of 78 mmol/24 hours (4.6 g salt/day) and a fall in systolic blood pressure of 4.97 mmHg, and in diastolic blood pressure of 2.74 mmHg.

Miller *et al* (1983) studied 16 healthy husband-wife pairs (men aged 40 years, women aged 37 years) to determine the effect on blood pressure of a reduction in dietary sodium from 152.7 (SE 10.1) mmol/day to 69.5 (SE 4.5) mmol/day for periods up to 12 weeks. In the men blood pressure decreased from 102/71 mm Hg to 99/68 mm Hg, and in women from 114/77 mm Hg to 109/73 mm Hg. There was no change in potassium excretion or body weight. There was variability in the blood pressure response amongst individuals and in 24 of 31 systolic blood pressure decreased, whereas 7 of 31 showed no decrease. In one person there was an increase that achieved statistical significance. Individuals with higher initial blood pressure were more likely to respond with a decrease in blood pressure. The decrease in blood pressure was significantly correlated with the magnitude of the sodium restriction ($r=0.36$, $p<0.03$)

Whelton *et al* (1998) carried out a trial of non-pharmacological interventions in the elderly to determine whether weight loss or reduced sodium intake was effective in treatment of older persons with hypertension. The study comprised 975 older people aged 60 to 80 years with systolic pressure <145/85 mm Hg, receiving treatment with single hypertensive medication. There were 585 obese and 390 non-obese subjects. The goal for sodium reduction was to maintain an intake below 80 mmol/day (1800 mg/day), based upon measurements made by 24 hour urine collection. The objective was to reduce the medication being given to reduce blood pressure medication and follow up was up to 30 months. The results showed that a 30% reduction in the need for antihypertensive therapy was achieved by reducing the average sodium intake by about 40 mmol/day, and by decreasing body weight on average by 3.5 kg. Best blood pressure control was achieved with combined interventions of both sodium reduction and weight reduction.

The strongest evidence that a change in dietary sodium leads to a change in blood pressure, with or without other dietary changes, in normotensive and hypertensive individuals, who are white or black, comes from the Dietary Approach to Stop Hypertension-sodium trial (DASH-sodium) (Sacks *et al*, 2001). The original DASH trial explored the effect of a diet rich in vegetables and fruit compared with a standard American diet. In the DASH-sodium trial the effect of a diet rich in vegetables and fruit and containing low-fat dairy products was compared with a standard American diet, and for each dietary pattern the level of salt was modified at three levels, high (about 150 mmol/day), intermediate (about 100 mmol/day) and low (about 50 mmol/day). 412 persons were randomly assigned to the control or DASH, foods at the three levels of sodium intake for 30 consecutive days. Actual consumption was assessed from 24 hour urinary excretion of sodium. The urinary sodium in the three groups was 144 mmol/day for the high groups, 106 mmol/day for the intermediate, and 65 mmol/day for the low, indicative of good compliance. At all levels of salt intake those on the DASH diet had significantly lower blood pressure than those on the control diet. When the sodium intake was reduced from the high to the intermediate level of consumption there was a reduction in systolic blood pressure by 2.1 mmHg in control and 1.3 mm Hg during DASH. When the sodium intake was reduced from the intermediate level to the low level of consumption there was a reduction in systolic blood pressure by 4.6 mm Hg in control and 1.7 mm Hg during DASH. As compared with the control diet high in sodium, the DASH diet low in sodium led to a mean systolic blood pressure which was 7.1 mm Hg lower in those without high blood pressure and 11.5 mm Hg in those with high blood pressure.

The level of dietary sodium had approximately twice as great an effect on blood pressure on the control diet compared with the DASH diet, for every level of intake. As the level of sodium intake was lowered progressively the response in terms of a lower blood pressure was greater. Consumption of the DASH diet compared with control diet resulted in a significantly lower systolic blood pressure at every level of

sodium consumption, and the effect on blood pressure was greater at high sodium levels than at lower sodium levels. The effect was seen in those with and those without hypertension, but was greater in those with hypertension.

The relationship between dietary sodium consumption and blood pressure has also been investigated in short-term salt loading studies. Murray *et al* (1978) observed consistent increases in blood pressure when normotensive human adult subjects were subjected to a sodium intake greater than 800 mmol/day, but Roos *et al* (1985) were unable to detect consistent changes in blood pressure with intakes as high as 1200 mmol/day.

Luft *et al* (1979) studied 14 normotensive healthy male volunteers (age 32 years, range 18-40 7 white and 7 black), who were given different levels of salt supplementation, 10 mmol/24 hours for 7 days, and 300, 600, 800, 1200, 1500 mmol/24 hours for 3 days each. In 6 subjects the study was repeated on a sodium intake of 1500 mmol/24 hours, while urinary potassium losses were replaced on a 24 hour basis. Urine was collected throughout for each 24 hour period, and echocardiography was used to measure cardiac size and function. The subjects experienced no ill effects, other than some diarrhoea at the highest levels of salt consumption which was corrected when water consumption increased. Total sodium excretion approached total sodium intake by 72 hours. There was considerable variability in the response within individual subjects. Most developed a significant increase in both systolic and diastolic blood pressure with the higher sodium intake, although there was no increase in a few. In white subjects the increase in blood pressure was significant at an intake of 1200 mmol/day, relative to the baseline of 10 mmol/day, whereas black subjects developed significant increased blood pressure by 800 mmol/day. Overall blood pressure increased significantly for sodium intakes between 10 and 1500 mmol/24 hours from 113 to 131 mm Hg systolic, and for sodium intakes between 10 and 1200-1500 mmol/24 hours from 69 to 85 mm Hg diastolic. There was a significant linear regression relationship between urinary sodium excretion and increase in blood pressure ($y=111.5 + 0.0083$ x: $r=0.48$, $p <0.001$).

There was no consistent change in plasma sodium or potassium concentration, but there was an increase in body weight of up to 5 kg. Cumulative potassium balance became negative on day 10 or 11 in subjects taking more than 600 mmol Na/day with a net deficit of -163 mmol or more. The effects of high sodium intake were attenuated when the study was repeated with subjects taking supplements of potassium to correct for urinary losses of potassium. Blood pressure returned to baseline values within 3 days of the completion of the study. It was concluded that blood pressure can be raised acutely in normotensive men by increasing sodium consumption to very high levels.

Myers *et al* (1982) reported a study in 136 normal individuals, aged 10 to over 60 years of age who were randomly assigned to an intake of sodium which was either 70 mmol/day or 200 mmol/day for periods of 14 days. Adherence was checked from urinary measurements and weight and blood pressure were recorded at the end of each study period. There was a significant increase in blood pressure for the group as a whole. The proportion which might have been considered to be hypertensive increased from 14 on the lower salt intake to 23% on the higher salt intake, which was more marked in the older people (13 to 50%) than in the younger people (0 to 4%).

3.2.2.4. Cardiovascular risk

He *et al* (1999) reported a prospective cohort study based upon the NHANES of 1971-75, in those aged 25 to 75 years, of whom 2688 were overweight and 6797 were normal weight. Sodium consumption estimates were based on a single 24 hour recall for dietary sodium. Over a period of 19 years of follow up there were 680 stroke events (210 fatal), 1727 coronary events (614 fatal), 895 cardiovascular disease deaths and 2486 deaths from all causes. Among overweight people, 100 mmol higher sodium intake was associated with 32% increase in stroke incidence, 89% increase in stroke mortality, 44% increase in coronary heart disease mortality, 61% increase in cardiovascular disease mortality and 39% increase in mortality from all causes. Dietary sodium was not significantly associated with cardiovascular disease risk in non-overweight persons. It was concluded that the effects on mortality and morbidity were greater than could have been expected from a simple effect on blood pressure. This raised the possibility of an independent direct effect of sodium intake on cardiovascular disease. Obesity activates the sympathetic nervous, the renin-angiotensin systems and causes insulin resistance and hyperinsulinaemia, and alters intra-renal vascular resistance. Therefore, these changes separately or together may have been related to enhance renal tubular sodium reabsorption and sodium retention.

In a prospective study of 1173 Finnish men and 1263 women aged 25-64 years, an increase in urinary sodium of 100 mmol/day was associated with hazard ratio for coronary heart disease, 1.51;

cardiovascular disease, 1.26; all cause mortality, 1.26 (Tuomilehto *et al*, 2001). The frequency of acute coronary events rose significantly with increasing sodium excretion and body mass index. High sodium intake predicted mortality and risk of coronary heart disease independent of other coronary risk factors, including blood pressure. There was direct evidence of harmful effects of high salt intake in the adult population. The median intake for men was 205 mmol/day, and for women, 154 mmol/day. Quartiles of excretion for men were <159, -205, -262, >262 mmol/24 hours; and for women <119, -154, -194, >194. Sodium was a more powerful predictor of mortality in men who were overweight.

In a prospective study in Japan, the relationship between deaths from stroke and sodium intake was assessed using a semi-quantitative food frequency questionnaire in 13,355 men and 15,724 women (Nagata *et al*, 2004). There were 269 deaths from stroke, and after controlling for covariates, there was a significant positive relationship between stroke deaths and sodium intake: hazards ratio (HR) 3.85 between the highest and lowest tertile for sodium consumption for men. The relationship was less strong for women (HR 1.7), and of borderline significance. Thus, although there is some evidence of a direct relationship between consumption of salt and death from stroke which is independent of blood pressure and most marked in people with a higher body mass index (He *et al*, 1999; Nagata *et al*, 2004), the finding is not consistent for all studies (Kagan *et al*, 1985; Alderman *et al*, 1998; Tuomilehto *et al*, 2001).

4. DOSE-RESPONSE ASSESSMENT

There are data which indicate that the human acute consumption of large doses of sodium chloride, such as 0.5 to 1.0 g per kg body weight can have fatal consequences, but these doses are far greater than those generally consumed on a habitual basis. The ingestion of concentrated solutions of sodium chloride can lead to local gastrointestinal irritation and mucosal damage, both in rodents and humans. This has been considered to increase the susceptibility to the carcinogenic effects of other carcinogens, such as nitrosamines, infection with *H. pylori*, or inadequate protection against free radical induced damage both in rodents and humans. Based on data collected in the Intersalt population study, no increased stomach cancer mortality was reported with the sodium intakes less than 2.7 g/day for men and 2.1 g/day for women. High concentration of salt may indirectly damage, through physical effects, DNA or chromosomes of bacterial and mammalian cells *in vitro*.

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 sodium 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. This is a continuous relationship which embraces the levels of salt habitually consumed, and continued benefit is seen at levels of salt consumption which are much lower than have been recommended as targets for population consumption (SACN, 2003; WHO/FAO, 2003). The character of the dose response can be modulated by a range of factors which include other components of the diet, relative weight, and level of physical activity, as well as fixed factors which include age, gender and genotype. It is not possible to determine a threshold level of habitual sodium consumption below which there is unlikely to be any adverse effect on blood pressure.

The evidence for adverse cardiovascular effects of sodium, which is supported by number of prospective studies, indicate an association of increased risk of morbidity and mortality from cardiovascular diseases, including coronary heart disease and stroke, with increasing sodium intake. While it has been suggested that the magnitude of the observed effects was greater than could have been expected from a simple effect on blood pressure, there is no direct evidence for this, and evidence that high sodium intake may have a direct adverse effect on left ventricular structure and function, independent of any secondary effect due to changes in blood pressure, is not conclusive.

CONCLUSIONS AND RECOMMENDATIONS

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

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

2. RISK CHARACTERISATION

The habitual intake of sodium for populations across Europe is high and exceeds the amounts required for normal function. The current levels of sodium 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 consumed in the diet (SACN, 2003; FNB, 2004; WHO, 2003 and 2004).

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