DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: June 1, 2016

From: Division of Biotechnology and GRAS Notice Review (HFS-255) Sodium Team

Subject: Salt Taste Preference and Sodium Alternatives

To: Administrative Record - Sodium Reduction Voluntary Guidance

Introduction

Sodium Reduction Overview

The Strategies to Reduce Sodium Intake in the United States Institutes of Medicine (IOM) Report (2010) notes that achieving lower intakes of excessive sodium should be a critical public health focus for all Americans and that excess sodium content in processed foods and restaurant menu items should be gradually reduced to a safer level. The Healthy People 2020 objective, Nutrition and Weight Status-19, is to "reduce consumption of sodium in the population aged 2 years and older" to a population target of 2,300 mg per day or less, consistent with the 2015-2020 Dietary Guidelines for American's dietary intake recommendations and Healthy People 2020.[1] The 2015-2020 Dietary Guidelines estimated average intake of sodium for all Americans ages two years and over as approximately 3,400 milligrams per day[2]. The Sodium Intake in Populations: Assessment of Evidence IOM Report (2013) reaffirmed that even the subset of the evidence on sodium intake involving direct health outcomes continues to support population-based efforts to reduce excessive sodium intake in the U.S. population. Consistent with these goals and findings, the U.S. Food and Drug Administration (FDA or we) supports efforts to create a broad, effective, and sustainable reduction of excessive sodium in the food supply, which will support recommendations for reducing the population intake of dietary sodium.

FDA's sodium reduction voluntary guidance is exploring good practices for sodium reduction in the food supply, expressed as measurable voluntary goals for sodium content (from sodium chloride, commonly called "salt," as well as other sodium-containing ingredients) in commercially processed, packaged, and prepared foods . The goals are designed to support reductions in excess sodium added to the food supply, keeping in mind the importance of sodium in food for microbial safety, stability, and other technical effects.

Our goals should be applicable to all foods with respect to technical challenges and opportunities. However, we particularly encourage attention by food manufacturers whose products make up a significant proportion of national sales in one or more of our food

[1] http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=29

[2] The 2015-2020 Dietary Guideline recommendation to limit intake of sodium to less than 2,300 mg per day is the upper intake level (UL) for individuals ages 14 years and older set by the IOM. The recommendations for children younger than 14 years of age are the IOM age- and sex-appropriate ULs. The DGA estimate of population dietary sodium intake is from 20075-200106 NHANES data.

categories, as well as restaurant chains that are national or regional in scope. This focus on market leaders reflects our desire to ensure that reformulations that may be undertaken by industry, and the burden they represent, will mainly occur where they will have the most impact on population sodium intake and public health. By creating a shared understanding of what meaningful sodium reduction would look like, and by establishing a common vocabulary for describing it, the goals are intended to promote a level playing field and to complement and coordinate existing efforts by food manufacturers and restaurant/food service operations.

The process for developing these goals involves three steps. First, the food supply is organized into categories (discussed in section 2 of FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance). A subset of categories ("target categories") are selected for goal assignment. The target categories are the subject of the subsequent steps in the process and are often referred to more generally as categories. Second, baseline sodium concentrations are calculated for each category (discussed in section 3 of FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance). Third, quantitative goals are assigned to each food category (discussed in sections 4 and 5 of FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance).

Salt Taste Preference and Sodium Alternatives

To further support this effort, we have surveyed available information on the technical functions of salt and other sodium containing ingredients, which are briefly discussed in this document. Food preservative functions are discussed in the memoranda "**Survey of Microbiological Issues in FDA-Regulated Products"** and "**Survey of Microbiological Issues in Meat and Poultry Products.**" These review memoranda are not prescriptive or comprehensive, particularly given the proprietary nature of many relevant food technologies, but represent a survey of the literature and may only discuss certain population groups. The purpose of these documents is to illustrate the existence of available food technologies that may be useful in sodium reduction, and to provide context for the proposed quantitative sodium reduction goals. Additional technologies and strategies may be identified through public discussion of our sodium reduction voluntary guidance and incorporated into future review documents.

Salt[3] is the primary sodium ingredient used in processed food and therefore makes the greatest contribution to sodium intake in the United States. The complex role of salt in processed foods makes its reformulation challenging. In addition, consumers tend to assume that sodium reduction produces less appealing products. This assumption emphasizes the importance of ensuring that products with lower sodium concentrations remain palatable to consumers and are successful in the marketplace. The mechanism of salty taste and the innate or learned preference for it is not entirely understood, but the role of salt in food preference has been widely recognized. Food companies are responding to the challenge with innovative solutions that can assist in reducing sodium. Increased understanding of structure and function of the salt receptors, the physiology of taste perception, and the psychology of sensory preference will assist the food industry in reducing sodium in processed foods.

[3] The focus of this document is 'sodium'. 'Salt' refers specifically to the compound sodium chloride, which is the most common source of sodium.

It is clear there is no single ingredient or technology that can serve as a universal substitute for salt. In addition to directly reducing sodium, many strategies and ingredients could be used to reduce sodium in foods, including modification of the shape and distribution of salt crystal, use of other salty-tasting ions, use of flavor enhancers, use of sodium ion channel modifiers, etc. However, sodium reduction solutions generally must be found on a product or product category basis. This document compiles some of the available public research on the physiological mechanism of salty taste and human preference for salt as well as research on potential strategies for maintaining acceptable flavor profiles when sodium content is reduced.

Background

Salt plays several important roles in food; it serves as a seasoning for flavor, and is important for microbiological stability for safety and spoilage prevention. It controls fermentation processes, imparts desirable textures and mouth-feel in foods, assists in color stability of meats, and serves as an essential nutrient (Durack *et al*., 2008). These myriad of functions in food have made salt an indispensable food ingredient throughout human history. Due to its broad utility and affordability as an ingredient, it is not unexpected that salt is widely consumed in excess of base nutritional requirements.

The general consensus from dietary intake data is that the bulk of dietary sodium is contributed through the consumption of processed food products and not from salt added at the table or other sources (water, supplements, etc.) (Henney *et al*., 2010). As a result, reduction of sodium in the food supply could result in reduced sodium intakes and improved public health outcomes. Over recent years, programs have been initiated to reduce sodium in processed foods in several countries including Canada, the United Kingdom, Australia, and Finland. More recently, the New York City Department of Health and Mental Hygiene in the United States also initiated a voluntary National Sodium Reduction Initiative. To ensure that the food industry can participate in efforts of this kind and continue to produce foods that appeal to consumers and maintain market share, it is important to continue exploring salt's role in flavor, taste preference, and food palatability. Moreover, recognizing the benefits and limitations of current sodium reduction strategies may help facilitate future solutions.

Methodology

Our review included both scientific and trade literature. We searched PubMed, Web of Science, and Google Scholar to compile scientific literature. We did not restrict publication dates or set geographic or language restrictions. General search terms included "sodium reduction technologies," "flavor modifiers," and "salty taste." Specific terms (e.g. "potassium chloride") mentioned in review articles from initial searches were then used for additional filtering. We also used commercial websites, press releases, and trade journals to gather company-specific information on sodium reduction technologies. We initially compiled approximately 200 references, of which; 109 that we found most relevant in illustrating potential sodium reduction and flavor compensation strategies were further examined.

Data Gaps

Some details of salt-replacement ingredients (exact composition/ingredients, mode of activity, etc.) could not be obtained given the proprietary nature of the technology which may be held as trade secrets by the manufacturers. We attempted to obtain such information where available by reviewing patents, publications, and press releases. In addition, information on the cost of salt-substitute ingredients is not publicly available. While it is commonly understood that these ingredients are more expensive than salt, the magnitude of the expense cannot be quantified for this review. Lastly, it is difficult to quantify market adoption of specific salt replacements because these ingredients may be labeled collectively as "artificial flavor" on packaged food ingredient statements without identifying specific components.

Literature Review

Mechanism of Salty Taste

Salt plays an important role in the flavor profile of a food for several reasons, most notably because it induces the perception of salty taste as part of a complex system, which involves various salt receptors. A specific ion channel in the membrane of particular cells within the taste bud appears to play a significant role in this process. Sodium and lithium are able to pass through the channel, while larger ions, such as potassium, magnesium, and calcium, cannot (Mattes, 1997; Bufe and Meyerhof, 2006). Furthermore, when this channel is blocked by the substance amiloride, salt perception is reduced. The role of this selective channel in salt perception helps explain why larger ions do not create an identical perception of saltiness. There is ongoing debate about the dominance of this perception mechanism in humans, based largely on variable interspecies inhibition of salt taste perception by amiloride (Smith and Margolskee, 2006). It is possible that this variation may be due at least partly to structural differences in the location and number of ion channels in humans relative to that in rodents, rather than differences in ion channel function (Brand and Huque, 2011). However, potassium, magnesium, and calcium are capable of imparting some salt flavor, which supports the theory that there are supplementary mechanisms for salt taste perception.

Understanding Salty Taste Preference

Whether the preference for salt is innate or learned has been the subject of much research, including both human feeding studies and animal model experiments. The development of both taste and smell has been reviewed extensively by Mennella and Beauchamp (2006). More specifically, the human preference for salt has been reviewed by Leshem (2009).

Salt preference appears to develop during the first two years of life. Studies on newborn infants, while not definitive, show them to be somewhat indifferent to salt, when measured by intake relative to water or facial expression (Beauchamp and Moran, 1986). No studies published to date have found the taste of salt to be attractive to extremely young infants (Mennella and Beauchamp, 2006). However, increased preference for salty water over plain water is seen as early as four months of age. This may be due to the maturation of the underlying mechanisms of salty taste perception and not due to any type of learned behavior. Further, developmental research has indicated that by 18 months children have developed more mature preferences, rejecting salted water but preferring salted foods (Beauchamp and Moran, 1984). These findings suggest that the context of the salty stimulus is important to preference. Several studies have shown that humans exhibit the preference for salt in foods and not the pure element, in contrast to other animals. Severely sodium-deprived volunteers showed a desire for more salty foods, but did not exhibit a specific sodium appetite analogous to thirst and the desire for water (Beauchamp *et al*., 1990; Mennella and Beauchamp, 2006).

Interestingly, perinatal exposure to salt may play a role in our future preference for it. Young adults whose mothers retrospectively reported morning sickness also had an increased preference for salt (Crystal and Bernstein, 1995). The authors speculate that maternal volume depletion and electrolyte imbalances associated with episodes of vomiting are responsible for the observed salt preference of their offspring. Adolescent children who had been inadvertently fed chloride-deficient formula as infants displayed a heightened preference for salty foods (Stein *et al*., 1996). Maternal sodium deprivation has also been linked to life-long heightened sodium preference of offspring in a rat model (Galaverna *et al.,* 1995).

Salt intake appears to affect changes in salt sensitivity and preference in complex ways. Higher salivary sodium concentration may reduce salty taste sensitivity and taste threshold. Salivary sodium concentrations exhibited a detectable inverse relationship with taste sensitivity in one study (Delwiche and O'Mahony, 1996). In another study, rapid salt depletion over 10 days by use of diuretics and low-sodium foods produced increased preference for salty foods, but not increases in salt taste sensitivity (Beauchamp *et al*., 1990). A third study found that short-term addition of salt to food, but not intake of salt tablets, increased preference for salty foods. This suggests that taste perception rather than simple salt intake is responsible for the reported changes in preference (Bertino *et al*., 1986).

Salt and Food Palatability

Aside from the obvious contribution to the sensation of salty taste itself, salt possesses several other functions that impact the palatability of food products. It is well known that salt enhances sweetness, suppresses bitterness and sourness, and leads to "well-rounded" flavor profiles (Fabian and Blum, 1943; Keast and Breslin, 2003).

The enhancement of sweet taste in the presence of salt has long been remarked, but has only recently begun to be understood. Oral taste cells in mice have been found to require the presence of sodium in order to transport glucose into the cell, providing one possible explanation for the phenomenon (Yee *et al*., 2011).

Sodium salts, including those withanions other than chloride, have been shown to suppress the bitterness of multiple compounds, independent of their salty taste. That is, a less salty-tasting sodium salt, such as sodium acetate, suppresses bitter taste to the same degree as sodium chloride (Breslin and Beauchamp, 1995; Breslin and Beauchamp, 1997; Nakamura *et al*., 2002).

Sodium Reduction: Renewed Interest and Strategies

Recent interest in sodium reduction has brought both time-tested and promising new food technologies to the forefront. Potential strategies for reducing sodium content include:

- Reduction of sodium without compensation or substitution;
- Reduction of sodium by physical modification of salt to increase perceived saltiness;
- Reduction of sodium by introducing direct mineral salt substitutes; and
- Reduction of sodium and compensation with other ingredients intended to enhance flavor.

A key goal of these strategies is to lower sodium content without sacrificing consumer acceptance. They are discussed below.

Sodium Reduction without Compensation or Substitution

Several strategies can be used to reduce the level of salt in a product formulation without substitution or compensation. Modest reductions in sodium content are often unnoticed by the consumer. Companies may not publicize their sodium reduction efforts with respect to specific products; this type of sodium reduction is sometimes referred to as "stealth reduction." Companies use step-wise gradual reduction to allow their customers to become accustomed to modest reductions in sodium before pursuing further reformulation (General Mills, 2010; Kraft Foods, 2010). Stealth reductions rely on the premise that modest decreases in saltiness are not noticeable in many cases, and that consumers will adapt over time to the reduction in salty taste so that their preferred salt level decreases. For example, Bertino *et al* (1982) showed this to occur in subjects whose entire diet was reduced in sodium.). It has also been shown that *ad libitum* salt use does not compensate for low sodium diets (Breslin *et al*, 1997, Sherpherd *et al,* 1989). The percent reduction that can be achieved by gradual unadvertised sodium reduction varies widely depending on the product. Generally, products with more complex flavors can reduce sodium content more without decreasing consumer acceptance. Products (i.e. cottage cheese) where the main flavor is heavily dependent on the salty taste will be somewhat more limited (Drake *et al*., 2011).

The validity of gradual sodium reduction and sensory acclimation has been addressed in several studies. In these specific examples, the sodium content of one processed food was reduced slowly over time without changing the sodium content of other constituents of the diet. The salt content of bread was reduced by 5% each week for 6 subsequent weeks to a 25% total reduction in total sodium without decreases in acceptance (Girgis *et al*., 2003). The salt content of chili was reduced by 40% without a reduction in subject acceptance. Interestingly, the subjects were able to identify the reduced sodium products in triangle tests[4], but were not averse to them in preference tests (Mitchell *et al*.,2011).

Some companies have chosen to publicize their sodium reduction strategies for marketing purposes, though sometimes with limited success (Gibeson, 2011; Scott-Thomas, 2011). Consumers often assume that reduced sodium foods lack flavor. Furthermore, large decreases in sodium are likely to be detected by consumers, especially if they are flagged on the product packaging (Ruusunen *et al*.,1999; Drake *et al*., 2011).

Physical Modification of Salt to Increase Perceived Saltiness

There are several strategies that focus on changing the physical properties of salt in ways that increase perceived saltiness without altering chemical identity. For example, changing the location and distribution of the added salt can increase flavor perception while decreasing total concentration. Contrasts in salt concentration, such as surface application or heterogenous mixing, can enhance the perceived intensity of salt. Salt delivered locally in high doses can increase perceived saltiness perception despite lower overall concentrations. Small surface salt crystals elicited higher perception of salt on a mixture of cooked ground

[4] A study design in which a consumer is asked to determine which of three items is not similar to the other two.

meat and fat minced into a spreadable paste, known as "paté", than large surface crystals or salt that had been incorporated homogeneously into it (Shepherd *et al*.,1989). Salty chicken pieces in reduced sodium broth were perceived to have the same amount of sodium as homogeneously salted soup (Dotsch *et al*.,1989). Dotsch *et al.* hypothesize that the increased residence time in the mouth for the chicken allowed more salt to be released and perceived by the consumer. Additionally, short and intense bursts of salty taste may reduce salt adaptation and increase perception (Busch *et al*.,1989).

As another example of the physical modification approach, changes to the structure of salt crystals themselves can increase their surface area, lower bulk density, and result in more sensory impact than traditional salt crystals. One example currently being marketed is a hollow multi-faceted salt crystal that claims to have a greater and more rapid solubility. The salt is available in many size preparations for various uses. When used for topical seasoning applications, an increased and more rapid solubility in saliva is reported to lead to a desirable "burst" of salty taste (Cargill, 2011). Using this product allows for reduction in sodium content of between 50 to 80% in bakery products (Watson, 2009 (a,b)). Producers of the modified salts may claim to reduce salt by 50% in cheddar cheese, while retaining "the same taste and shelf-life" as traditional products (Watson, 2010).

A recent study found that salt could be reduced through substitution with air bubbles in model gel systems (Goh *et al*., 2010). The air bubbles served as bulking agents, which allowed the salt to be reduced by 40% and still achieve an equivalent level of perceived saltiness. Such applications may be limited to matrices that can adequately support the stability of the air bubbles.

Another way to physically modify the release of salt from a food matrix is through encapsulation (e.g. coating of particles with another material). Potential "wall" materials for coated salt particles include lipids, proteins and carbohydrates. Encapsulation has been used for decades to manipulate the release of volatile flavor ingredients, and has found applications for less volatile substances working on the taste receptors, such as prolonging sweetener or coolant release from chewing gum (Reinecciu, 2006). The additional processing steps necessary to achieve an encapsulated product can be quite expensive. It is possible that the low-cost nature of salt has not justified such a value-added process.

The use of emulsions in which salt can be incorporated into the aqueous phase has also been explored. Effectiveness may depend on other ingredients in the system and therefore optimization for individual products is necessary (Leatherhead Food Research, 2005).

<u>Direct Substitution with Other Mineral Salts</u>

Potassium Chloride

While there is currently no perfect replacement for salt, many ingredient and flavor companies have lines of products which can be substituted for salt on a one-to-one basis. The most common bulk substitute is potassium chloride (KCl) (Dotsch *et al*.,1989). Some consumers do perceive KCl to have a bitter aftertaste, which limits its applications in substituting for sodium salt (Frank and Mickelsen, 1969). Published studies on salt reduction commonly use KCl.

KCl substitution at 20 - 40% appears to have a minimal flavor impact in many cases, depending on the specific food system (Cauvain, 2007; Champagne et al., 1991; Kilcast and den Ridder, 2007). In one study, Collins (1997) reported that sectioned and formed hams prepared with a 70/30 ratio of NaCl/KCl were not different in terms of flavor, tenderness and overall acceptability compared to hams made with 100% salt. Another study on fermented sausages found no significant alteration in texture from KCl substitution for NaCl; however, a taste panel found that substitution levels at or above 30% began to introduce bitterness (Gou et al., 1996). In the manufacture of bread, the impact of KCl on yeast activity and dough rheological properties is similar to that of the sodium salt but there may be adverse impacts on flavor once salt substitution exceeds 10 - 20% (Cauvain, 2007). Demott et al. (1984) reported that a taste panel gave comparable scores to full-sodium and 50% KCl-substituted cottage cheeses.

The mechanism that makes the potassium cation taste salty appears to be different from that of sodium as the perception of potassium salts is generally not affected by amiloride blockading, but is affected for sodium salts (Ye *et al*., 1991; Ye *et al*., 1993; Lindemann, 1996). As with sodium salts, potassium salts of anions larger than chloride exhibit less salty taste (Murphy *et al*., 1981; Delwiche *et al*., 1999). The larger salts may not able to diffuse through the tight junctions between individual cells in the taste bud as easily as smaller molecules (Ye *et al*., 1993). This causes less potassium to reach basolateral receptors and additionally causes a diffusion potential across the junction which inhibits the taste cell activation (Ye *et al*., 1991; Ye *et al*., 1993). To combat this, KCl is often used in sodium salt blends and combined with salt, flavor modifiers, bitter blockers, flavors, and amino acids to reduce undesirable attributes. For example, Gou et al. (1996) found that in dry-cured pork loins, KCl and potassium lactate used in concert could replace 40% of NaCl without any significant detrimental effect to flavor.

The encapsulation strategy discussed in the previous section may also be useful for deploying mineral salt substitutes. Potential off-flavors could be disguised via encapsulation with salt or other masking agents (Bell, 1985). Encapsulation may be used in current commercial salt substitution strategies, but this information is difficult to ascertain as the modified ingredient would not be listed explicitly as “encapsulated” on the ingredient statement.

Another application of encapsulation may be useful for reducing salt in water-in-oil emulsions (Frasch-Melnik *et al*.,2010), such as emulsions where fat crystals are used for stabilization (i.e. margarine, butter spreads, etc.). Further, using double layer emulsions, it may be possible to “hide” potassium chloride or other salt substitutes inside the inner aqueous phase to disguise their off-flavors, to allow concentration of sodium on the outer parts of the aqueous phase of the emulsion (Frasch-Melnik *et al*.,2010).

Mineral Salt Blends

Sea salt and reduced sodium sea salt have recently become popular ingredients among food companies seeking to introduce products perceived as lower in salt but retaining consumer appeal. There is a broad perception among consumers that sea salts are universally lower in sodium content. Some products specifically state the source of their proprietary sea salt (i.e. Dead Sea or Mediterranean Sea). These salts are generally a blend of mineral salts (magnesium, calcium, and/or potassium) which effectively displace sodium ((Dotsch *et* *al*.,1989)). Metal ions present in natural sea salt are often claimed to be the reason for the unique taste of specialty salts, though until recently this evidence was anecdotal and inconclusive (Smillie, 2002). Blending can create a sea salt containing 60% less sodium than ordinary table salt, however, the sodium concentration of sea salt can be highly variable, with some having more sodium than table salt on an equivalent-weight basis (Pszczola, 2007; Drake and Drake, 2011).

Drake and Drake (2011) examined 38 sea salts and several commercial salt substitutes in solution with a trained taste panel. The composition of other minerals (calcium, potassium, magnesium, iron, zinc) was quite variable as well across types and locations of origin. They found some salts to have volatile aromatics, likely as a result of the method of drying, as well as sour, bitter, umami, and astringent taste attributes. When salty taste was compared on the basis of sodium concentration, some sea salts did show greater salty intensity as well as differing time-intensity profiles. Drake and Drake suggest that the other mineral components of the salts did play a role in enhancing the salt taste intensity. Yang and Lawless (2005), found that zinc salts possessed an umami quality ("glutamate-like sensation"), giving support to this theory.

Other mineral salts, such as magnesium sulfate, magnesium chloride, calcium lactate, and calcium chloride, were found to be mildly salty when presented to a trained sensory panel. They also had an umami (see discussion below) component. However, they were found to be bitter and metallic (Lawless, 2003). These undesirable aspects are likely to limit their scope of use and concentration as salt replacers.

One product recently evaluated in FDA's generally recognized as safe (GRAS) notification program is a co-crystallization product of magnesium chloride hexahydrate, ammonium chloride, and potassium chloride which forms a specific triple salt. The notifier's GRAS determination concluded that it could be used to partially substitute sodium salt (up to 60%) in a wide range of applications from commercial processed foods to at-home use. It may also retain the preservative properties of salt (Smart Salt, 2011).

<u>Sodium Reduction and Compensation with Flavor Modifiers</u>

As the options for direct substitution of sodium salt are limited, so it is helpful to also consider use of substances that can amplify salty taste and flavors that are added or already present in the product. Substances that are able to change, enhance, suppress, and augment flavors and taste, without exhibiting a flavor or taste of their own, are known as flavor or taste modifiers (Matheis, 1999). Here, we use the term "flavor modifier" in reference to any substance that performs any of these functions. The term flavor modifier is often used interchangeably with flavor potentiator, flavor enhancer, and flavor modulator, as there are no standardized definitions of these terms (Kemp and Beauchamp, 1994). Flavor enhancer is defined by the Codex Alimentarius Committee (CAC) to be "a food additive, which enhances the existing taste and/or odor of the food" (Codex Alimentarius Committee, 1989). Flavor modifiers can be used to increase salty taste perception without increasing salt content. Many flavor modifiers cannot replace salt; they only increase the "salt perception" present in the product. It is possible that modifiers/enhancers increase response of the salt receptors. This interaction may be "on site" at the receptor or "off-site" within the protein matrix. Several flavor modifiers which may be used include sodium salts such as monosodium glutamate, disodium inosate and disodium guanylate. Though used in small quantity, they enhance the overall flavor impact and alter salt perception.

Umami

Umami taste has been a part of Asian cuisine in the form of mushrooms, kelp, fish, and soy sauces for centuries. As ingredients, these foods are widely used to increase the palatability of other foods. L-(+)-glutamic acid (glutamate), one of the amino acids responsible for the umami taste, was first isolated from seaweed in 1908 and determined to be the source of the unique flavor attributes possessed by similar types of foods (Kinnamon, 2009). The sodium salt of glutamic acid, monosodium glutamate (MSG), was commercialized shortly thereafter using microbial cultures. Monosodium L-glutamate was determined to be GRAS in 1980 (21 CFR 182.1). Eventually umami was recognized as its own unique taste sensation—not a combination of the other four basic tastes (Yamaguchi *et al.,* 2000). It is often described as "savory," "meaty," or "brothy," and translated literally it means "delicious" (Yamaguchi *et al.,* 2000; Kinnamon, 2009). In the 60 years following the isolation of glutamate, two ribonucleotides were identified, inosinate-5'-monophosphate (IMP) and guanylate-5'-monophosphate (GMP), which also exhibited umami flavor and had synergistic activity with glutamate (Reineccius, 2006; Beauchamp, 2009; Kinnamon, 2009). Various other umami flavor enhancers have also been independently determined to be GRAS for flavor use by Flavor and Extract Manufacturers Association (FEMA) (Leffingwell, 2011, Leffingwell, 2014).

Sensory studies have supported the potential use of MSG to reduce sodium in some foods with congruent flavors (i.e. savory) (Yamaguchi *et al.,* 1984; Chi and Chen, 1992; Fuke, 1996). The sodium content in mass percent of MSG is roughly 3 times lower (12%) than in salt (39%), however, this presence of sodium may limit the scope of its usefulness. The physiological mechanism that is responsible for the umami taste of glutamate and other compounds is not entirely understood (Brand, 1942; Lindemann, 2000; Chaudhari *et al.,* 2009). Interaction with several G-protein coupled receptors has been put forth as plausible mechanisms (Chaudhari *et al.,* 2000; Lindemann, 2000; Chaudhari *et al.,* 2009; Kinnamon, 2009). It has also been suggested that the umami receptor has two binding sites, which could explain the synergism between glutamate and 5'-nucleotides (Fuke, 1996; Rolls *et al.,* 2004).

Commercially available umami ingredients vary widely in form and origin. Yeast extract, fermented milk proteins, mold fermentation by-products, and sea plant extracts are all sources of savory tasting compounds which can be used for sodium reduction applications and are currently on the market. Lee (2011) details information about a combination of sea plant extracts, which in a water solution are 65% as salty as salt, containing 43% less sodium; they also contain umami compounds which may enhance the salt perception of reduced sodium foods (Lee, 2011). Few studies have been published to highlight the success of these ingredients in food formulations, however.

The umami taste of soy sauce has been attributed to free amino acids (in addition to glutamate and salt) by several studies (Lioe *et al*., 2007; Lioe *et al*., 2010). Fractionation of soy sauce and sensory analysis revealed that the most umami fractions contained lower molecular weight compounds including di- and tri-peptides (<500 daltons). Succinic acid is also a component of soy sauce (discussed below), which may contribute to its umami taste.

Strings of amino acids (di- tri- and tetra- peptides and larger) have also been described in the literature as inducing an umami or savory taste. Generally, these peptides have L-glutamic acid at the N-terminal site (Lioe *et al*., 2010). These peptides are often formed from hydrolysis of animal, fungal (yeast), or vegetable proteins.

Other Amino Acids

Many amino acids and their derivatives have been explored as both a means to enhance salty flavor and to reduce bitterness of potassium and other salt substitutes. Three amino acids (histidine, arginine, and lysine) with basic groups were all found to have some salty taste properties, though they may also have bitter and "sharp" properties (Schiffman and Dackis, 1975). However, several other studies report that these amino acids to have no taste (Kirimura *et al*., 1969; Solms, 1969).

Many patents have been issued for the use of amino acids as salt enhancers/replacers. Several companies hold patent for the combination of salt, L-aspartic acid, and L-arginine, which they claim can increase the taste of salt "about 10 to 50%" (Lee, 1992). A patent for the use of lysine with KCl to reduce bitterness and enhance salty taste was granted in 1999 (Kato *et al*., 1989; Berglund *et al*., 1999).

Maillard Reaction Products

Reactions of reducing sugars and amino groups during the Maillard reaction can result in the formation of compounds that may potentially elicit the umami taste sensation. Specifically, the reaction of glutamic acid and some reducing sugars to produce glutamate glycoconjugates, are reported to have umami taste comparable to that of MSG (Beksan *et al*., 2003; Schlichtherle-Cerny *et al*., 2003). There is very little published literature on the functionality of these compounds, but it seems they have potential to enhance salty flavor through their umami characteristics. It is also possible that during Maillard reaction, proteins decompose to amino acids and peptides responsible for the umami perception.

Kokumi

Certain "mouth-feel" characteristics of food, such as the "mouthfulness," "thickness," or "continuity," perceived by a consumer have been given the term "kokumi" by the Japanese (Schiffman and Dackis, 1975). Kokumi does not have a flavor of its own, but rather enhances the other five basic tastes. The mechanism of the taste-enhancing nature of kokumi compounds is attributed to extracellular calcium-sensing G-protein mediated receptors (CaSR) (Kirimura *et al*., 1969). Further, a calcium receptor-based screening method has been patented for isolation and identification of kokumi compounds (Solms, 1969). Di- and tri-peptides such as γ-L-glutamyl-2-aminobutyric acid have been shown to be CaSR agonists associated with the "mouthfulness" of kokumi (Futaki et al., 2012). In addition, kukami flavor enhancers have also been independently determined to be GRAS for flavor use by FEMA (Leffingwell, 2011, Leffingwell, 2014).

Several compounds said to be kokumi have been isolated from garlic, legumes, and Gouda cheese (Schiffman and Dackis, 1975; Lee, 1992; erglund and Alizadeh, 1999). A tasteless extract from beans was used to enhance the "mouthfulness and complexity" of broth and prolonged its savory flavor. The active compounds were identified as γ-L-glutamyl-L-leucin, γ-L-glutamyl-L-valine, and γ-L-glutamyl-L-cysteinyl-β-alanine (Lee, 1992). These peptides have been patented, and their use as flavor enhancers has been explored in chicken broth, cream cheese, and tomato juice (Kato *et al*., 1989). While the study of kokumi substances is still in its relative infancy, these compounds appear to have potential for use in reduced-sodium applications to compensate for the loss of salty flavor, specifically salt's ability to contribute "mouthfulness and complexity".

Cooling Compounds

Chewing gum, mints, and toothpaste commonly contain substances used to provide a cooling sensation. Menthol, menthyl lactate, and others (several of them patented) are commonly used. More recently, menthylamides (WS-5 and WS-3) and butanamides (WS-23, ICE 6000, and ICE 10,000) with coolant properties orders of magnitude greater than that of menthol are now of commercial importance as coolants. Recently, it has been recognized that at low levels of ICE coolants enhance salty flavor (some at even sub-threshold levels) (Drahl, 2009). Their use in broth at concentrations below the threshold of direct perception to enhance salty flavor was described in a patent by Gray *et al*., (2008). The amount of reduction that could be achieved was not specified, however. A blend of ICE coolants, called ICE-1500, is currently being marketed for use as a flavor and saltiness enhancer in salsas, salad dressing, marinades, margarine, soup, bouillon, and alcoholic beverages at levels from 0.5-12 ppm. Concentrations for "cooling" applications are in the 100-500 ppm range (Qaroma, 2011).

Acids

The interaction between salty and sour tastes has potential to be exploited to increase salty taste. Many studies have investigated the effect of acids (below and above threshold level) on salty taste. There appears to be indications that low levels of acid increase salty taste perception, while high levels suppress it (Fabian and Blum, 1943; Pangborn and Trabue, 1967; Keast and Breslin, 2002). Structure/function studies have found "ideal" taste-enhancing substances to contain two negative charges optimally spaced between 4 and 6 carbons (Ney, 1971). Succinic acid, a component of yeast extracts and other protein hydrolysates, fits this structural requirement and has been shown to have umami properties (Velisek *et al.,* 1978).

In one study by Hatae *et al*, (2009) black rice vinegar present in a water solution at a concentration of one-half the salt threshold decreased the taste and recognition threshold of salt by 3-fold. Black rice vinegar had a larger effect than white rice vinegar, possibly due to the increased level of free amino acids and glutamate in the black rice vinegar in addition to the acid (Lioe *et al.,*2007). Further, the perceived salty taste of reduced-salt rye bread was increased when acetic acid was included in the formulation (Hellemann, 1992). Additionally, tomato juice was also perceived as saltier by a trained panel when low levels of citric acid (up to 0.4%) were added to the formulation (Pangborn and Chrisp, 1964). The same relationship occurred in lima bean puree (Pangborn and Trabue, 1964).

Salts of lactic acid have been shown by some studies to possess a marked saltiness. The saltiness of potassium lactate, however, is marred by bitterness; it may be possible to use limited amounts of sodium chloride (2% concentration) to mask the bitterness is a possibility (Brewer *et al.,* 1995). Lactate salts (specifically sodium lactate), with approximately 20% sodium, have been used in processed meat products for flavor enhancement and are GRAS for this purpose (21 CFR 184.1768) as they are said to complement spices and other flavors. They can also contribute to extended shelf-life (Desmond, 2006).

Trehalose

The mildly sweet disaccharide sugar trehalose (composed of two α-D-glucose units connected via a 1,1-linkage), is said to enhance the salty taste of NaCl and mask off-tastes associated with KCl (Ganesan et al., 2007). The mechanism for its mode of flavor enhancement is not known. However, a gene that encodes for a G-protein coupled receptor that exhibited binding affinity for trehalose was discovered in fruit flies and may provide a starting point for further investigation of the mechanism (Ishimoto *et al.,* 2000).

Several patents have been granted for trehalose as a flavor enhancer. One such patent was granted to Uchida *et al*., (2000) for the use of trehalose from 3-9% of the total solution with salt concentrations from 1.5-12%. This provided the best flavor enhancing effect. The high concentration of trehalose necessary to enhance salty taste, however, may potentially limit its widespread applicability and be cost prohibitive. Researchers were able to increase salty perception 1.2-2 times that of a pure salt solution using trehalose within the optimal concentration range, which amounted to at least a 17% reduction in sodium. Trehalose also enhanced umami taste in the presence of MSG. The potential usefulness of trehalose is highlighted in seasoning blends, soy sauce, and other sauces with high salt contents, soups, and salted meats in this patent.

An additional patent was filed for the use of trehalose in amounts less than 1.5% in the final concentration in the food, in conjunction with KCl and NaCl by Ganesan *et al*., (2010). This would be useful for products containing lower amounts of added salt. Applications for potato chips, popcorn, chili, broth, marinated poultry, and other foods with 50% reduced salt were highlighted in the patent. In addition, sensory scores showed many of the applications to be acceptable when KCl, NaCl, and trehalose were added.

Thaumatin

The intensely sweet protein thaumatin, which is usually isolated from the katemfe fruit, may also be useful at sub-sweetness threshold concentrations as a flavor enhancer that may aid in salt reduction. According to suppliers, it is useful in savory products, and it may allow up to 30% reductions in sodium content while creating well-rounded flavors and enhancing spicy notes (Naturex, 2010). Its usefulness for sodium reduction strategies stems from its ability to suppress and mask bitter notes associated with KCl (Green, 1999). In the U.S., it was self-determined to be GRAS as a flavoring ingredient in 2009. There is no evidence that thaumatin is currently widely used in foods for sodium reduction. However, it can be labeled as a flavor, so there is no straightforward way to assess the true level of market penetration.

Sodium Channel Activators

Most strategies to reduce the sodium content in packaged foods focus solely on the substance responsible for producing the salty taste. Alternately, there is potential to manipulate the perception of salty taste at the receptor level. For example, one U.S.-based company has pioneered a cell-based assay method capable of processing many samples in a short time to screen for substances that interact with taste receptor cells (Sheridan, 2004). Using this method adapted from the pharmaceutical industry, they have discovered a small molecule, (*N*-(2-hydroxyethyl)-4-methyl-2-(4-methyl-1*H*-indol-3-ylthio)pentanamide, dubbed “S3969”, that reversibly binds and activates the epithelial sodium channel, causing improved flux of sodium across the membrane (Lu *et al.,* 2008).

This high throughput research methodology is not limited solely to salty taste enhancement; the previously-mentioned firm is exploring molecules that activate sweet and umami receptors as well, which may be useful in compensating for reduced sodium or indirectly enhancing saltiness. As of 2004, they had over 170 pending patent applications, with 29 U.S. patents issued (Sheridan, 2004) This patent portfolio appears to have led to licensing agreements with a number of food companies (Senomyx, 1996). Thus far, these compounds have been considered to be "flavors" and have been independently determined to be GRAS for flavor use by FEMA.

Odor-Flavor Interactions and Natural Flavors

Interactions between taste, odor, and other modalities all contribute to flavor. For this reason, it may be possible to compensate for reduced salty taste using other sensory cues (Watson, 2009(b)). As one example of this approach, odor and volatile flavor compensation have some potential to assist in sodium reduction. Herbs and spices, particularly those of high quality with well-preserved volatile compounds, could be used for this purpose. However, these and other volatile ingredients are not always economically feasible, particularly for use in high concentrations.

Added flavors must be congruent with salty taste in order to achieve the desired effect (Noble, 1996; Djordjevic *et al.*, 2004). Lawrence *et al.* found savory odors (i.e., sardine, ham, bacon, anchovy, chicken, peanuts, and others) to increase the perceived intensity of salty solutions, dependent on the odor quality and perceived strength (Lawrence *et al.*, 2009). Lawrence and colleagues further tested some of these odorants in cheese (Lawrence et al., 2011). Comte cheese (made from unpasteurized cow milk) and sardine flavors were able to enhance salty taste in mozzarella-type cheese. Both sardines and cheese contain di- and tri-peptides that are likely affecting salt perception.

Conclusion

Flavor and taste are key drivers of consumer purchasing and acceptance. The depth of our physiological understanding of salty and related savory tastes and taste preference continues to improve. With greater understanding, the food industry may be able to expand the range of food technologies that allow sodium to be reduced without causing decreases in consumer acceptance.

Reduction of added salt in processed foods is a challenging process because of the many functions of salt. However, it is clear from press releases and label comparisons that some companies are gradually reducing sodium without loss of consumer acceptance A variety of tools and strategies, some of which are described in this document, are available, and incremental approaches to reduction have great potential to reduce sodium in the food supply without alienating customers. Sea salt, potassium chloride, and herbs and spices are currently being used widely as ingredients in product formulations to reduce sodium. These ingredients are appearing in marketing campaigns and on product packaging of companies who have chosen to publicize their sodium reduction efforts.

Flavor modifiers, including various umami compounds, may also be used for sodium reduction. These ingredients can be used to increase salty perception, and interest and research into these appears to be increasing based on published literature and patents. Umami compounds do not exhibit clean saltiness and may alter the overall sensory perception of a formulation, however, so their usefulness may be limited to specific types of foods. It is difficult to know how often these types of compounds are being used exclusively for sodium reduction as they have other desirable flavor effects and be listed only as flavor on the ingredient statement.

At the receptor level, some flavor modifiers have been found to interact with cells in the taste bud and cause improved flux across the epithelial sodium channel. Additionally, compounds that bind to receptors for other primary tastes (umami, sour, etc.) that enhance salty taste are also viable approaches to increase saltiness perception. Several biotechnology firms are using high-throughput assays to identify receptor-modulating chemicals more efficiently. Given the financial potential of these discoveries and the number of new patents and scholarly articles that are being published, it appears this is one direction in which the industry is investing heavily.

It is not clear how widely the sodium reduction strategies described in this document are being used. While some companies have spoken publicly about their sodium reduction initiatives, few mention the exact strategies they use to achieve these goals. In addition, many ingredients used in sodium reduction are listed as flavor or can serve other functions aside from sodium reduction so it is challenging to estimate specific use. Disappearance (poundage) data for ingredients is one way to gain insight on this question, although it is impossible to determine whether an ingredient is being used exclusively for sodium reduction.

None of the sodium reduction options presented in this memorandum is a perfect substitute and there is no single solution that will work for all food applications. As new technologies develop and as our understanding of the receptors responsible for salty and savory tastes improves, new ingredients may become available that can preserve consumer acceptance in reduced salt food formulations. This technological capability can complement and buffer the adaptation of consumer taste preference over time that could occur if sodium content of the food supply were to be gradually reduced. Our voluntary goals are consistent with incremental reduction of sodium over time, which can support the adaptation of taste preferences and the exploration and implementation of new food technologies.

References

1. Beauchamp GK, Bertino M, Burke D, Engelman K. Experimental sodium depletion and salt taste in normal human volunteers. *American Journal of Clinical Nutrition.* 1990;51:881.
2. Beauchamp GK, Moran M. Acceptance of sweet and salty tastes in 2-year-old children. *Appetite.* 1984; 5:291.
3. Beauchamp GK, Moran M. Developmental Changes in salt acceptability in human infants. *Developmental Psychobiology*. 1986;19:17-25.
4. Beauchamp GK, Pearson P. Human development and umami taste. *Physiology and Behavior*. 1991;49:1009-1012.
5. Beauchamp GK. Sensory and receptor responses to umami: an overview of pioneering work. *American Journal of Clinical Nutrition*. 2009;90:723S.
6. Beksan E, Schieberle P, Robert F et al. Synthesis and Sensory Characterization of Novel Umami-Tasting Glutamate Glycoconjugates. *Journal of Agricultural and Food Chemistry.* 2003;51:5428-5436.
7. Bell AD, inventor; 1985. Salt substitute containing potassium chloride coated with a mixture of maltodextrin and salt and method of preparation. United States patent US 4,556,566.
8. Berglund KA, Alizadeh H, inventors. 1999. Composition and method for producing a salty taste. US Patent 5,897,908.
9. Bertino M, Beauchamp GK, Engelman K. Increasing dietary salt alters salt taste preference. *Physiology & Behavior.* 1986;38:203-213.
10. Bertino M, Beauchamp GK, Engelman K. Long-term reduction in dietary sodium alters the taste of salt. *American Journal of Clinical Nutrition.* 1982;36:1134.
11. Brand JG. Receptor and transduction processes for umami taste. *The Journal of Nutrition.* 2000;130:942S-945S.
12. Brand JG, Huque T, inventors. 2011. Human salty taste receptor and methods of modulating salty taste perception. United States Patent Application 2011/0236313 A1.
13. Breslin PAS, Beauchamp GK. Salt enhances flavour by suppressing bitterness. *Nature*. 1997;387:563.
14. Breslin PAS, Beauchamp GK. Suppression of bitterness by sodium: variation among bitter taste stimuli. *Chemical Senses*. 1995;20:609.
15. Brewer M, Gills L, Vega J. Sensory characteristics of potassium lactate and salt in a model system. *Journal of Sensory Studies*. 1995;10:73-87.
16. Bufe B, Meyerhof W. The human perception of taste compounds. In: Etierant P, Voilley A, Editors. *Flavour in Food*. Woodhead Publishing; 2006.
17. Busch JLHC, Tournier C, Knoop JE, Kooyman G, Smit G. Temporal contrast of salt delivery in mouth increases salt perception. Chemical Senses. 2009;34:341-348.
18. Cargill. Alberger® Brand Flake Salts. 2011. http://www.cargill.com/salt/products/food-manufacturing/alberger-brand-flake-salts/index.jsp. Accessed February 11, 2011.
19. Cauvain SP. Reduced salt in bread and other baked products. In: Kilcast, David; Angus, Fiona, Editors. *Reducing Salt in Foods - Practical Strategies*. Woodhead Publishing. 2007:pp-pp.
20. Champagne CP, Fontaine J, Dussault F and Delaquis PJ. 1993. Effect of partial replacement of NaCl by KCl on the fermentative activity of mixed starter cultures for meat fermentation. *Food Microbiology*. 1993;10:329-35.

21. Chaudhari N, Landin AM, Roper SD. A metabotropic glutamate receptor variant functions as a taste receptor. *Nature Neuroscience*. 20003:113-119.
22. Chaudhari N, Pereira E, Roper SD. Taste receptors for umami: the case for multiple receptors. *The American Journal of Clinical Nutrition*. 2009;90:738S.
23. Chi S, Chen T. Predicting optimum monosodium glutamate and salt concentrations in chicken broth as affected by spice addition. *Journal of Food Processing and Preservation*. 1992;16:313-326.
24. Codex Alimentarius Committee. Codex class names and the international numbering system for food additives. CAC/GL 36-1989. 1989. ftp://ftp.fao.org/codex/meetings/CCFAC/CCFAC31/INS_e.pdf . Accessed February 11, 2011.
25. Collins JE. Reducing salt (sodium) levels in process meat poultry and fish products. In: A.M. Pearson and T.R. Dutson, Editors. *Advances in meat research, Production and processing of healthy meat, poultry and fish products* Vol. 11, Blackie Academic & Professional, London; 1997:283–297.
26. Crystal SR, Bernstein IL. Morning sickness: impact on offspring salt preference. *Appetite*. 1995;25:231-240.
27. Delwiche J, O'Mahony M. Changes in secreted salivary sodium are sufficient to alter salt taste sensitivity: Use of signal detection measures with continuous monitoring of the oral environment. *Physiology & Behavior*. 1996;59:605-611.
28. Delwiche JF, Halpern BP, DeSimone JA. Anion size of sodium salts and simple taste reaction times. *Physiology & Behavior*. 1999;66:27-32.
29. Demott B.J., Hitchcock JJ and Sanders OG. Sodium concentration of selected dairy products and acceptability of a sodium substitute in Cottage cheese. *Journal of Dairy Science*. 1984; 67 (7):1539–1543.
30. Desmond E. Reducing salt: A challenge for the meat industry. *Meat Science*. 2006;74:188-196.
31. Djordjevic J, Zatorre RJ, Jones-Gotman M. Effects of perceived and imagined odors on taste detection. *Chemical Senses*. 2004;29:199-208.
32. Dotsch A, Busch J, Batenburg M. Strategies to reduce sodium consumption: a food industry perspective. *Critical Reviews in Food Science and Nutrition*. 2009;49:841-851.
33. Drahl C. Seeking Saltiness. *Chemical & Engineering News*. 87[22], 29-30. 2009..
34. Drake S, Drake M. Comparison of salty taste and time intensity of sea and land salts from around the world. *Journal of Sensory Studies*. 2011;26:25-34.
35. Drake S, Lopetcharat K, Drake M. Salty taste in dairy foods: Can we reduce the salt? *Journal of Dairy Science*. 2011;94:636-645.
36. Durack E, Alonso-Gomez M, Wilkinson MG. Salt: A review of its role in food science and public health. *Current Nutrition & Food Science*. 2008;4:290-297.
37. Fabian F, Blum H. Relative taste potency of some basic food constituents and their competitive and compensatory action. Journal of Food Science 1943;8:179-193.
38. Frank RL, Mickelsen O. Sodium-potassium chloride mixtures as table salt. *American Journal of Clinical Nutrition*. 1969;22:464.
39. Frasch-Melnik S, Norton IT, Spyropoulos F. Fat-crystal stabilised w/o emulsions for controlled salt release. *Journal of Food Engineering*. 2010;98:437-442.
40. Frasch-Melnik S, Spyropoulos F, Norton IT. W1/O/W2 double emulsions stabilised by fat crystals-formulation, stability and salt release. *Journal of Colloid and Interface Science*. 2010; 350(1):178-185.

41. Fuke S, Ueda Y. Interactions between umami and other flavor characteristics. *Trends in Food Science & Technology.* 1996;7:407-411.
42. Galaverna O, Nicolaidis S, Yao SZ, Sakai RR, Epstein AN. Endocrine consequences of prenatal sodium depletion prepare rats for high need-free NaCl intake in adulthood. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*. 1995;269:578.
43. Ganesan K, Zoerb H, Mullally G, Weigle D, Adams T, inventors. 2007. Ingredient systems comprising thehalose, food products containing trehalose, and methods of making same. United States patent application 2007/0292593..
44. General Mills. General Mills to further reduce sodium across portfolio. 2010. http://www.generalmills.com/en/ChannelG/NewsReleases/Library/2010/April/Sodium_Reduction.aspx . Accessed February 11, 2011..
45. Gibeson A. Sodium reduction strategies. Food Business News. February 7, 2011.
46. Girgis S, Neal B, Prescott J. A one-quarter reduction in the salt content of bread can be made without detection. *European Journal of Clinical Nutrition.* 2003;57:616-620.
47. Goh SM, Leroux B, Groeneschild CAG, Busch J. On the effect of tastant excluded fillers on sweetness and saltiness of a model food. *Journal of Food Science*. 2010;75:S245-S249.
48. Gou P, Guerrero L, Gelabert J, Arnau J. Potassium chloride, potassium lactate and glycine as sodium chloride substitutes in fermented sausages and in dry-cured pork loin. *Meat Science.* 1996;42(1):37–48.
49. Gray K, Yeep GL, Ellerman RG, inventors. 2008. Salt enhancement. United States patent application 2008/0311266.
50. Green C. Thaumatin: A natural flavour ingredient. In: Corti A, Editor. *Low-Calorie Sweeteners: Present and Future: World Conference on Low-Calorie Sweeteners, April 25-28, 1999, Barcelona, Spain*. Basel, Switzerland: Karger; 1999;129-132.
51. Halpern BP. Glutamate and the flavor of foods. *The Journal of Nutrition*. 2000;130:910S-914S.
52. Hatae K, Takeutchi F, Sakamoto M, Ogasawara Y, Akano H. Saltiness and acidity: Detection and recognition thresholds and their interaction near the threshold. *Journal of Food Science*. 2009;74:S147-S153.
53. Hellemann U. Perceived taste of NaCl and acid mixtures in water and bread. *International Journal of Food Science and Technology*. 1992;27:201-211.
54. Henney J, Taylor C, Boon C. Strategies to reduce sodium consumption in the United States. 2010. Washington D.C., The National Academies Press.
55. Ishimoto H, Matsumoto A, Tanimura T. Molecular identification of a taste receptor gene for trehalose in *Drosophila*. *Science*. 2000;289:116-119.
56. Kato H, Rhue MR, Nishimura T. Role of free amino acids and peptides in food taste. In: Teranishi R, Buttery RG, Shahidi F, Editors; *Flavor Chemistry: Trends and Developments*, Volume 388. American Chemical Society; 1989:158-174.
57. Keast RSJ, Breslin PAS. An overview of binary taste-taste interactions. *Food Quality and Preference.* 2002;14:111-124.
58. Kemp SE, Beauchamp GK. Flavor modification by salt and monosodium glutamate. *Journal of Food Science*. 1994;59:682-686.
59. Kilcast D, den Ridder C. Sensory issues in reducing salt in food products. In: Kilcast D, Angus F, Editors. *Reducing salt in foods: practical strategies*. Boca Raton Boston, New York, Washington-DC: Woodhead Publishing Ltd; 2007:201-220.

60. Kinnamon SC. Umami taste transduction mechanisms. *American Journal of Clinical Nutrition.* 2009;90:753S.
61. Kirimura J, Shimizu A, Kimizuka A, Ninomiya T, Katsuya N. Contribution of peptides and amino acids to the taste of foods. *Journal of Agricultural and Food Chemistry.* 1969;17:689-695.
62. Kraft Foods. Kraft Foods plans to reduce sodium in North American products. PR Newswire. March 17, 2010. http://www.prnewswire.com/news-releases/kraft-foods-plans-to-reduce-sodium-in-north-american-products-an-average-of-10-percent-by-2012-88182702.html Accessed October 2011.
63. Lawless H. Sensory interactions in mixtures. *Journal of Sensory Studies.* 1986;1:259-274.
64. Lawless HT, Rapacki F, Horne J, Hayes A. The taste of calcium and magnesium salts and anionic modifications. *Food Quality and Preference*. 2003;14:319-325.
65. Lawrence G, Salles C, Palicki O, Septier C, Busch J, Thomas-Danguin T. Using cross-modal interactions to counterbalance salt reduction in solid foods. *International Dairy Journal*. 2011;21:103-110.
66. Lawrence G, Salles C, Septier C, Busch J, Thomas-Danguin T. Odour-taste interactions: a way to enhance saltiness in low-salt content solutions. *Food Quality and Preference*. 2009;20:241-248.
67. Leatherhead Food Research. Salt in Processed Foods. March 2005.
68. Lee GH. A salt substitute with low sodium content from plant aqueous extracts. *Food Research International*. 2011;44:537-543.
69. Lee T. Kraft General Foods I, assignee. 1992. Salt enhancer. United States patent 5,145,707.
70. Leffingwell J, Leffingwell D, Leffingwell & Associates. Flavor Properties of FEMA GRAS List 26 Flavor Chemicals. A Preliminary Assessment. Available at: http://www.leffingwell.com/gras26/FEMA%20GRAS%2026.pdf. Accessed on December 12, 2014.
71. Leffingwell J, Leffingwell D, Leffingwell & Associates. Flavor Properties of FEMA GRAS List 25 Flavor Chemicals. A Preliminary Assessment. Available at: http://www.leffingwell.com/download/PF_GRAS25-2.pdf. Accessed on December 12, 2014.
72. Leshem M. Biobehavior of the human love of salt. *Neuroscience and Biobehavioral Reviews*. 2009;33:1-17.
73. Lindemann B. A taste for umami. *Nature Neuroscience*. 2000;3:99-100.
74. Lindemann B. Taste reception. *Physiological reviews*. 1996;76:719.
75. Lioe HN, Selamat J, Yasuda M. Soy sauce and its umami taste: A link from the past to current situation. *Journal of Food Science*. 2010;75:R71-R76.
76. Lioe HN, Wada K, Aoki T, Yasuda M. Chemical and sensory characteristics of low molecular weight fractions obtained from three types of Japanese soy sauce (shoyu) - Koikuchi, tamari and shiro shoyu. *Food Chemistry* 2007;100:1669-1677.
77. Lu M, Echeverri F, Kalabat D et al. Small molecule activator of the human epithelial sodium channel. *Journal of Biological Chemistry*. 2008;283:11981.
78. Matheis G. Flavor modifiers. In: Ashurst P, Editor. *Food Flavourings*. 3rd Edition. Springer-Verlag; 1999;367-405.
79. Mattes RD. The taste for salt in humans. *American Journal of Clinical Nutrition.* 1997;65:692S.

80. Mennella JA, Beauchamp GK. Early flavor experiences: research update. *Nutrition Reviews.* 1998;56:205-211.
81. Mitchell M, Brunton NP, Wilkinson MG. Current salt reduction strategies and their effect on sensory acceptability: a study with reduced salt ready-meals. *European Food Research and Technology*. 2011;1-11.
82. Murphy C, Cardello AV, Brand JG. Tastes of fifteen halide salts following water and NaCl: anion and cation effects. *Physiology & Behavior.* 1981;26:1083-1095.
83. Nakamura T, Tanigake A, Miyanaga Y et al. The effect of various substances on the suppression of the bitterness of quinine, human gustatory sensation, binding, and taste sensor studies. *Chemical and Pharmaceutical Bulletin*. 2002;50:1589-1593.
84. Naturex. 2010. Those with taste choose Talin. http://www.thaumatinnaturally.com/food.html. Accessed September 2011
85. Ney KH. Flavor enhancing effect of L-glutamate and similar compounds. *Zeitschrift für Lebensmittel-Untersuchung und –Forschung*. 1971;146:141-143.
86. Noble AC. Taste-aroma interactions. *Trends in Food Science and Technology*. 1996;7:439-444.
87. Pangborn R, Trabue I. Detection and apparent taste intensity of salt-acid mixtures in two media. *Attention, Perception, and Psychophysics*. 1967;2:503-509.
88. Pangborn R, Trabue I. Taste Interrelationships. V. Sucrose, Salt, and Citric Acid in Lima Bean Puree. *Journal of Food Science*. 1964;29:233-240.
89. Pangborn RM, Chrisp R. Taste Interrelationships. VI. Sucrose, Salt, and Citric Acid in Canned Tomato Juice. *Journal of Food Science*. 1964;29:490-498.
90. Pangborn RM, Pecore SD. Taste perception of salt in relation to dietary intake of salt. *American Journal of Clinical Nutrition.* 1982;35:510.
91. Pszczola DE. Savoring the possibilities. *Food Technology*. 2007;61(4):55-66.
92. Qaroma, Inc. ICE 1500 (Liquid coolant). 2011. Ref Type: Online Source.
93. Reineccius G. *Flavor Chemistry and Technology*. Second Edition. Boca Raton, FL: CRC Press, 2006.
94. Rolls E, Critchley H, Wakeman E, Mason R. Responses of neurons in the primate taste cortex to the glutamate ion and to inosine 5'-monophosphate. *Physiology and Behavior.* 2004;59:991-1000.
95. Ruusunen M, Särkkä-Tirkkonen M, Puolanne E. The effect of salt reduction on taste pleasantness in cooked 'Bologna-type' sausages. *Journal of Sensory Studies.* 1999;14:263-270.
96. Schiffman SS, Dackis C. Taste of nutrients: amino acids, vitamins, and fatty acids. *Attention, Perception, and Psychophysics*. 1975;17:140-146.
97. Schlichtherle-Cerny H, Affolter M, Cerny C. Taste-active glycoconjugates of glutamate: New umami compounds. In: Hofmann T, Ho C-T, Pickenhagen W, Editors. *Challenges in Taste Chemistry and Biology*. Volume 867. American Chemical Society; 2003:210-222.
98. Scott-Thomas C. Campbell's to add back sodium to combat soup sales slump. *Food Navigator*. July 13, 2011. http://www.foodnavigator-usa.com/Suppliers2/Campbell-s-to-add-back-sodium-to-combat-soup-sales-slump
99. Senomyx. Senomyx collaborations. http://www.senomyx.com/flavor_programs/collaborations.htm. Accessed September 2011.

100. Shepherd R, Wharf SG, Farleigh CA. The effect of a surface coating of table salt of varying grain size on perceived saltiness and liking for pate. *International Journal of Food Science and Technology*. 1989;24:333-340.
101. Sheridan C. A taste of the future. *Nature Biotechnology*. 2004;22:1203-1205.
102. Smart Salt. GRAS Exemption Claim for Tri-Sal. GRN 000272. 2008. Ref Type: Report.
103. Smart Salt. Smart Salt in processed foods. http://www.smartsalt.com/processed-food-industry.html. Accessed September 2011.
104. Smillie D. Salt chic. *Forbes*. 2002. http://www.forbes.com/forbes/2002/1028/366.html
105. Smith D, Margolskee R. Making sense of taste. *Scientific American*. 2006;16:84-92.
106. Solms J. Taste of amino acids, peptides, and proteins. *Journal of Agricultural and Food Chemistry*. 1969;17:686-688.
107. Stein LJ, Cowart BJ, Epstein AN, Pilot LJ, Laskin CR, Beauchamp GK. Increased liking for salty foods in adolescents exposed during infancy to a chloride-deficient feeding formula. *Appetite*. 1996;27:65-77.
108. Uchida Y, Iritani S, Toshio M, inventors. 2000. Method for enhancing the salty-taste and/or delcious-taste of food products. United States patent 6,159,529.
109. Velisek J, Davidek J, Kubelka V, Tran TBT, Hajslova J. Succinic acid in yeast autolysates and its sensory properties. *Nahrung* 1978;22:735-743.
110. Watson E. 2009a. Small really is beautiful when it comes to salt replacement. *Food Manufacture*. April 29, 2009. http://www.foodmanufacture.co.uk/Business-News/Small-really-is-beautiful-when-it-comes-to-salt-replacement
111. Watson E. 2009b. Bakers slash salt with 'micro' salt particles. *Bakery and Snacks*. March 26, 2009. http://www.bakeryandsnacks.com/Ingredients/Bakers-slash-salt-with-micro-salt-particles
112. Watson E. Cheese trial next after bakers slash salt with 'micro' particles. *Food Manufacture*. August 11, 2010. http://www.foodmanufacture.co.uk/Ingredients/Cheese-trial-next-after-bakers-slash-salt-with-micro-particles
113. Yamaguchi S, Ninomiya K. Umami and food palatability. *The Journal of Nutrition*. 2000;130:921.
114. Yamaguchi S, Takahashi C. Interactions of monosodium glutamate and salt on saltiness and palatability of a clear soup. *Journal of Food Science*. 1984;49:82-85.
115. Yang H, Lawless H. Descriptive analysis of divalent salts. *Journal of Sensory Studies*. 2005;20:97-113.
116. Ye Q, Heck GL, DeSimone JA. The anion paradox in sodium taste reception: resolution by voltage-clamp studies. *Science*. 1991;254:724.
117. Ye Q, Heck GL, DeSimone JA. Voltage dependence of the rat chorda tympani response to Na+ salts: implications for the functional organization of taste receptor cells. *Journal of Neurophysiology*. 1993;70:167.
118. Yee K, Sukumarana S, Kothaa R, Gilbertson T, Margolskee RR. Glucose transporters and ATP-gated K+ (KATP) metabolic sensors are present in type 1 taste receptor 3 (T1r3)-expressing taste cells. *Proceedings of the National Academy of Sciences*. 2011;108(13):5431-5436.