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December 5, 2008

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BY:.....

Dr. Robert L. Martin
Deputy Division Director
Division of Biotechnology and GRAS Notification Review
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Dear Dr. Martin:

On behalf of Smart Salt, Inc. (Smart Salt), please find enclosed the GRAS Notification for Tri-Sal. This GRAS Notification is being submitted in accordance with the proposed rule issued in 1997 (62 FR 18938 - 18964; April 17, 1997) whereby an individual may inform the Food and Drug Administration of a determination that the use of a substance is GRAS. Tri-Sal has been determined on the basis of scientific procedures to be generally recognized as safe under the conditions of its intended use as a replacement for up to 50% of the sodium chloride added to foods during manufacture or by consumers to season foods. This application of Tri-Sal is, therefore, exempt from the requirement of premarket approval, Tri-Sal will be used in foods in general, including meat, poultry, and egg products, but excluding infant formula.

Should any questions arise regarding this submission, please do not hesitate to contact me. I can be reached via telephone at 202.730.4140; email at carrie.rabe@weinberggroup.com; or facsimile at 202.833.7057.

Very truly yours,

Carrie Rabe, Ph.D.
Senior Consultant
The Weinberg Group Inc.

CR/kw

Enclosures

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BY:.....

Smart Salt, Inc.

GRAS Exemption Claim for Tri-Sal

December 5, 2008

**Smart Salt, Inc.
1261 Prospect Street
Suite 9
La Jolla, CA 92037
Telephone: 619.817.1994**

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1.0 GRAS EXEMPTION CLAIM AND OVERVIEW

1.1 Claim of Exemption from the Requirement for Premarket Approval

Tri-Sal has been determined to be generally recognized as safe (GRAS) and, therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Taplo Maki
CEO
Smart Salt, Inc.
1261 Prospect Street
Suite 9
La Jolla, CA 92037

December 5, 2008
Date

1.2 Name and Address of the Notifier

Tapio Maki
CEO
Smart Salt, Inc.
1261 Prospect Street
Suite 9
La Jolla, CA 92037

Telephone: 858.456.2437
Fax: 858.456.2239
Email: tapio.maki@smartsalt.com

1.3 Common Name of the Notified Substance

The common name for the triple salt that is the subject of this notification is Tri-Sal.

1.4 Conditions of Use

Tri-Sal is intended to be used as a substitute for a portion of the sodium chloride used in foods. The purpose of the product is to lower sodium intake. Tri-Sal will be used in food in general, including meat, poultry, and egg products, but excluding infant formula.

1.5 Basis of GRAS Determination

Pursuant to 21 CFR 170.3, Tri-Sal has been determined to be GRAS by scientific procedures for its intended conditions of use. The safety of Tri-Sal is supported by the fact that the triple salt readily dissolves in aqueous media into the same constituent ions as the component salts that are used in its manufacture. Each of the component salts has been affirmed as GRAS by the US Food and Drug Administration: 21 CFR 184.1138, 184.1426, and 184.1622 for ammonium chloride, magnesium chloride, and potassium chloride, respectively, based on reviews by the Select Committee on GRAS Substances. Ammonium chloride is affirmed as GRAS as a "flavor enhancer," magnesium chloride as a "flavoring agent," and potassium chloride as both a "flavor enhancer" and "flavoring agent."

1.6 Availability of Information

All data and information that was used as a basis for this GRAS determination can be provided to the Food and Drug Administration (FDA) upon request, by contacting Tapio Maki.

2.0 DETAILED INFORMATION ABOUT THE IDENTITY OF THE NOTIFIED SUBSTANCE

2.1 Identity

Tri-Sal is a triple salt containing magnesium, ammonium, and potassium ions. Tri-Sal is being developed for use as a substitute for a portion of the sodium chloride that is used in foods. It is the product of co-crystallization of one part potassium chloride (KCl), 3 parts ammonium chloride (NH₄Cl), and 4 parts magnesium chloride hexahydrate (MgCl₂ · 6H₂O).

Chemical formula: MgCl₂ · 0.75NH₄Cl · 0.25KCl · 6H₂O

Empirical formula/structure: Mg²⁺ [Cl]₃ [K⁺]_{0.25} [NH₄⁺]_{0.75} [H₂O]₆

IUPAC name: Current IUPAC nomenclature rules do not have strict rules that allow creation of a single preferred name for the triple salt. The following alternative names may be used:

- 1) If IUPAC rules for naming addition compounds (IR-5.5 names of [formal] addition compounds) are used, the name would be:

Ammonium chloride-magnesium chloride-potassium chloride-water (3/4/1/24)

- 2) If naming is done in accordance with constitutional nomenclature, the stoichiometric name would be:

Ammonium magnesium potassium chloride hydrate, (NH₄)₃Mg₄KCl₁₂·24H₂O

Either name is valid and can be used interchangeably to define the salt.

CAS number: 1044829-32-4

Common name: Tri-Sal

Tri-Sal is proposed as the common name for the triple salt. There is no single readily identifiable IUPAC name by which the salt can be referred to in labeling. The names proposed under IUPAC naming conventions are likely to be confusing to consumers. The consumer cannot be expected to understand the stoichiometric notations that are part of both of the IUPAC names. Furthermore, a number of salt

substitutes¹ exist that contain some or all of the ions present in Tri-Sal, but not necessarily in the same ratio or crystalline composition. In order for the consumer to be able to identify Tri-Sal and distinguish it from other salts, the product needs a distinctive name like Tri-Sal. The Tri-Sal name is consistent with the concept that the product is composed of three salts. Smart Salt will assure transparency of the common name by providing information on the component salts on its website.

Empirical Formula: $MgCl_2 \cdot (NH_4Cl)_{0.75} \cdot (KCl)_{0.25} \cdot 6H_2O$

Molar Mass: 262.058 g/mol (hexahydrate)

2.2 Characteristic Properties

Appearance: White crystalline solid

Taste: Salty

Hygroscopy: Substantially nonhygroscopic (unlike its component chloride salts)

Solubility in Water: Very soluble (>1 g/mL)

2.3 Quantitative Composition

Tri-Sal is the product of co-crystallization of one part potassium chloride (KCl), three parts ammonium chloride (NH₄Cl), and four parts magnesium chloride hexahydrate (MgCl₂ · 6H₂O). The quantitative composition is presented in Table 1, below.

Table 1. Quantitative Composition

Materials	% (w/w)	Kg/batch
MgCl ₂ · 6H ₂ O	77.23	20.3305
NH ₄ Cl	15.55	4.092
KCl	7.22	1.901
Total	100.00%	26.3235

¹ Salt substitutes that contain potassium chloride alone or mixed with other salts include: AlsoSalt, Morton's Salt Substitute, Morton's Light Salt Mixture, No Salt, Nu Salt, Cardia Salt, and Lessalt.

2.4 Manufacturing Process

The triple salt is manufactured using food grade, FDA-affirmed GRAS materials. A summary of the three component salts that are used in the manufacture of the triple salt substance are provided below:

Magnesium chloride

IUPAC name:	Magnesium chloride
CAS number:	[7791-18-6] (hexahydrate)
Chemical formula:	MgCl ₂ .6H ₂ O (hexahydrate)
Molar mass:	203.31 g/mol (hexahydrate)
Appearance:	White or colorless crystalline solid
Density:	1.56 g/cm ³ (hexahydrate solid)
Melting point:	714°C (987 K)
Boiling point:	1,412°C (1,685 K)

Ammonium chloride

IUPAC name:	Ammonium chloride
CAS number:	[12125-02-9]
Chemical formula:	NH ₄ Cl
Molar mass:	53.49 g/mol
Appearance:	White solid
Density:	1.527 g/cm ³
Melting point:	338°C (sublimes)
Boiling point:	1,412°C (1,685 K)
Solubility in water	29.7 g/100 g water at 0°C

Potassium chloride

IUPAC name:	Potassium chloride
CAS number:	[7447-40-7]
Chemical formula:	KCl
Molar mass:	74.551 g/mol
Appearance:	White crystalline solid
Density:	1.987 g/cm ³
Melting point:	776°C
Boiling point:	1,412°C (1,685 K)
Solubility in water	28.1 g/100 cm ³ (0°C); 34.0 g/100 cm ³ (20°C); 56.7 g

Process Description

All starting materials for Tri-Sal meet food grade standards (Food Chemicals Codex; FCC). The starting materials for a 100-mole batch of Tri-Sal are as follows:

Table 2. Quantities of Components Used to Manufacture 100 Moles of Tri-Sal

	Formula weight	Moles	Kilograms	Pounds	Liters
MgCl ₂ x 6 H ₂ O	203.305	100	20.3305	44.821	
NH ₄ Cl	53.49	76.5	4.092	9.021	
KCl	74.55	25.5	1.9	4.1	
Water					9 - 12

Note: Decimals are added to avoid multiple approximations in up- or down-scaling. The values can be "rounded" in the final phase of the calculations.

All of the dry components are mixed first. Water is added to the mixed salts at a rate commensurate with the stirring efficiency of the system. The mixture is heated to the boiling point at normal pressure with stirring.² The solution is boiled to dissolve all of the components and to reach a balance between the salts. The water content is further evaporated under vacuum to reach a point in which 4 – 5 liters is left in the reactor. The salt mixture is cooled, filtered and dried at temperatures between 50°C and 80°C. Equipment suitable for handling slat is used to avoid colorization of the product. The yield is over 90% of the theoretical value.

2.5 Substance Specifications

Specifications for Tri-Sal are presented in Table 3.

Table 3. Substance Specifications*

Parameter	Acceptance Criteria
Mg (% w/w)	9.08 – 9.46
NH ₄ (% w/w)	5.06 – 5.26
K (% w/w)	3.66 – 3.81
pH (2% solution)	5.7 – 6.2
Color/Solution	White/Clear
Arsenic (As) max mg/kg	0.5
Lead (Pb) max mg/kg	2
Particle Size (mesh)	30-60
Moisture content (%)	<0.15

*An anticaking agent such as silicon dioxide, Aerosil, or calcium silicate is generally added to the product at 0.25% ± 0.05 % (w/w)

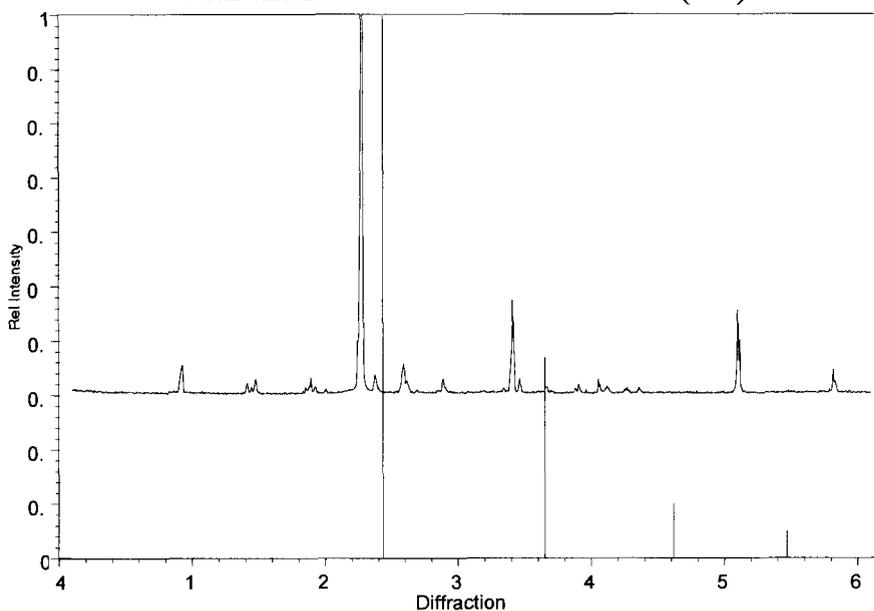
² It is not important that all of the components do not dissolve into the solution at this point in the manufacturing process.

2.6 Crystalline Composition

The manufacture of Tri-Sal uses three separate chloride salts. However, virtually none of the individual component salts are present in the finished product, indicating that the product is not a simple mixture of the individual salt components. The manufacturing process results in a triple salt with a uniform crystalline structure that differs from that of any of the component salts. This has been demonstrated using x-ray powder diffraction spectroscopy.

When the x-ray diffraction pattern of Tri-Sal powder³ was compared with the reference standard patterns stored in the Joint Committee on Powder Diffraction Spectroscopy (JCPDS) database, the patterns produced by the individual component salts were not present in significant amounts (Figures 1-3). Residual potassium chloride and magnesium chloride crystals are present at less than 1% in the triple salt and no residual ammonium chloride crystals are present.

Figure 1. XRD Pattern for the Triple Salt Sample Compared with the Pattern for Reference KC1 (red)



³ X-ray diffraction patterns of Tri-Sal were obtained by packing the powder and scanning from 5 to 65 degrees two-theta using Cu K-alpha radiation and a scintillation detector on a Philips Diffractometer at 30 kV and 20 mA.

Figure 2. XRD Pattern for the Triple Salt Sample Compared with the Pattern for Reference $MgCl_2$ (red)

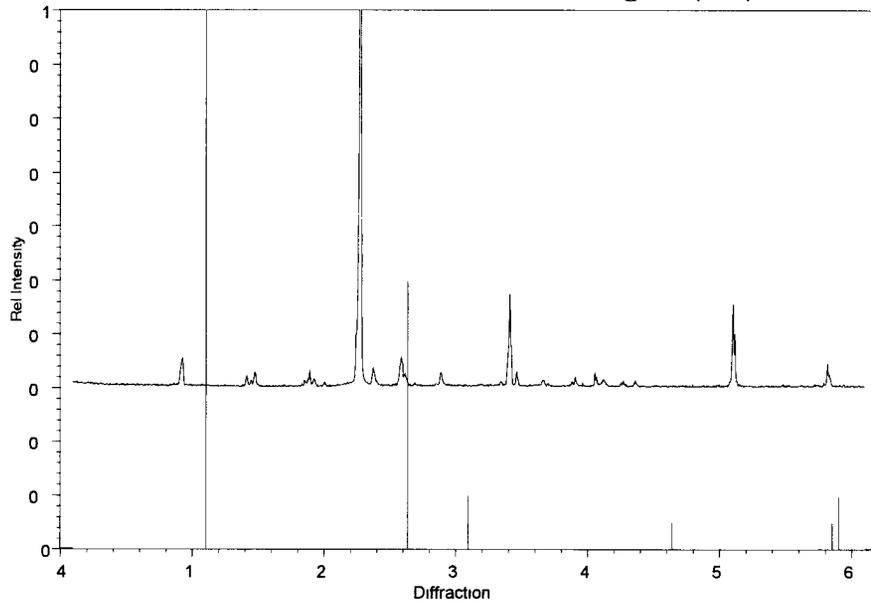
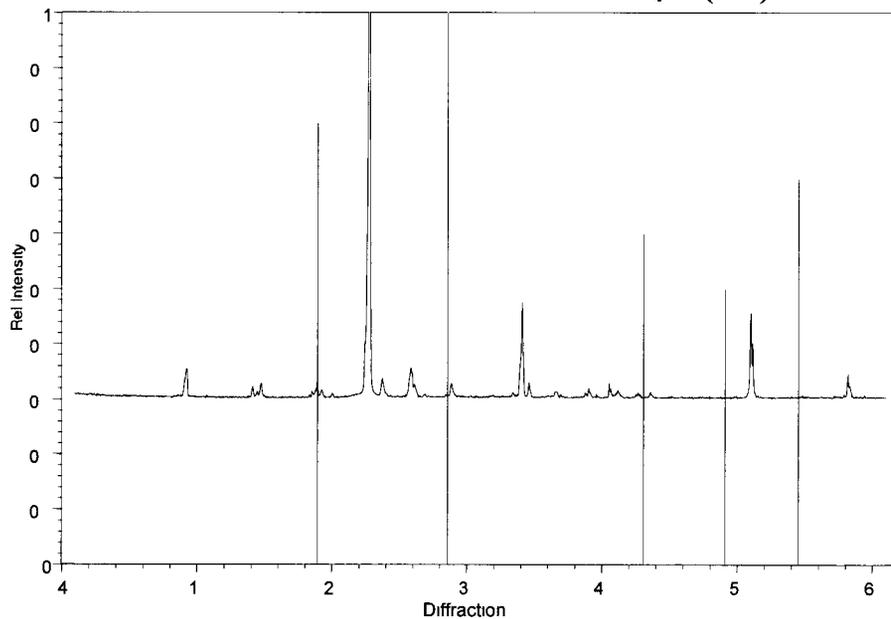


Figure 3. XRD Pattern for the Triple Salt Sample Compared with the Pattern for Reference NH_4Cl (red)



3.0 SELF-LIMITING LEVELS OF USE

Tri-Sal is intended for use as a 1:1 substitute for sodium chloride, but, because of palatability issues, it cannot be used as a 100% substitute. The taste of Tri-Sal when used alone is not equivalent to sodium chloride. Palatability of a variety of foods was demonstrated to be good in a study by the National Food Labs following replacement of 25% of the added sodium chloride by an equal amount (w/w substitution) of Tri-Sal (National Food Labs 2008). At very high levels of substitution for sodium chloride (e.g., >50%), the palatability of foods seasoned with Tri-Sal will limit its level of use.

4.0 BASIS FOR GRAS CONCLUSION

4.1 Overview

Tri-Sal is a triple salt of magnesium chloride, ammonium chloride, and potassium chloride that has a unique crystalline structure. Tri-Sal also has a technical property (i.e., less hygroscopicity) that allows it to be more conveniently used in food manufacturing and as an ingredient in table salt substitutes than mixtures of the individual component salts. However, because it dissolves readily in aqueous media to the same individual ions (i.e., magnesium, potassium, ammonium, and chloride) as the component salts from which it is manufactured, prior determinations of the safety of the individual component salts or component ions accurately predict the safety of crystalline Tri-Sal.

Several groups of recognized experts have evaluated the safety of the component salts and component ions present in Tri-Sal (Table 4). These include assessments by the Select Committee on GRAS Substances (SCOGS); the Joint Expert Committee on Food Additives (JECFA); Europe's Scientific Committee on Foods (SCF), and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board of the Institute of Medicine (IOM).

Table 4. Expert Evaluations of the Safety of the Components of Tri-Sal

Substance Evaluated	Expert Group Performing the Evaluation	Reference
Magnesium salts	SCOGS	FASEB 1976
	JECFA	WHO 2007
Potassium salts	SCOGS	FASEB 1979
	JECFA	WHO 1980
Ammonium salts	SCOGS	FASEB 1974
	JECFA	WHO 1980
Magnesium ions	IOM	IOM 1997
	SCF	SCF 2006
Potassium ions	IOM	IOM 2005b
	SCF	SCF 2006

Based on the findings of these experts, replacement by Tri-Sal of up to 50% of the sodium chloride consumed by individuals at the 90th percentile of salt intake would reasonably be expected to be safe. The bases for these conclusions are presented below.

4.2 Intended Use and Exposure Estimate

The intended use of Tri-Sal is as a flavoring or flavor enhancer. Tri-Sal is intended to be used as a partial substitute for sodium chloride in foods. The addition of Tri-Sal to foods allows manufacturers and consumers to add less sodium chloride to foods without reducing the saltiness of the foods. Tri-Sal can be substituted 1:1 for a portion of sodium chloride in foods, but is not

expected to be a 100% replacement for sodium chloride because of palatability issues when used alone or as a high proportion of the regular salt content of foods.

It is anticipated that Tri-Sal will be utilized by both food manufacturers and individual consumers. The manufacturers are expected to use Tri-Sal to reduce the sodium content of processed foods so that labeling claims such as "reduced or less sodium,"⁴ "low sodium,"⁵ or other approved sodium-related nutrient content claims⁶ may be utilized (21 CFR 101.61). It is also anticipated that salt blends containing both sodium chloride and Tri-Sal may be used by health-conscious consumers who wish to lower their sodium intake during food preparation and at the table to season foods.

The sole use of Tri-Sal is as a replacement for a portion of the sodium chloride in the diet. Therefore, potential exposure to Tri-Sal may be estimated using current data on sodium chloride consumption data by the US population.

According to the National Academy of Science's Institute of Medicine (2005a), the National Health and Nutrition Examination Survey (NHANES) data (i.e., NHANES III 1988-1994⁷) shows that the intake of sodium chloride from food (not including salt added at the table) varied by sex and age group (Table 5).

Table 5. Sodium Chloride Intake From Food (Excluding Table Salt)

	Range Across All Age Groups ^{1,2} (g/day)	
	Male	Female
Median	7.9 – 11.9	5.8 - 7.9
90 th Percentile	11.4 – 15.7	8.9 – 11.7

¹ Aged 9 and over

² Calculated from sodium intake (i.e., sodium intake × [m.w. sodium chloride/m.w. sodium])

The Institute of Medicine reports that approximately 6% of the daily intake of salt is from use of salt at the table (IOM 2005a). If the daily intake values shown in Table 5 are increased by 6% to account for table salt added during meals, the daily intakes would increase as shown in Table 6.

⁴ At least 25% less sodium per reference amount than an appropriate reference food.

⁵ 140 mg of sodium or less per reference amount (per 50 g if reference amount is small)

⁶ For example, "light in sodium," "very low sodium," or "lightly salted."

⁷ Values for sodium intake from NHANES III ranged from 3.1 g/day to 4.7 g/day for men and 2.3 g/day to 3.1 g/day for women at the median and 4.5 g/day to 6.2 g/day for men and 3.5 g/day to 4.6 g/day for women at the 90th percentile. Median sodium intake data from NHANES from 1999-2000 are similar (3.3 g/day to 4.0 g/day for men and 2.3 to 2.9 g/day for women; Ervin et al. 2004).

Table 6. Sodium Chloride Intake From Food (Including Table Salt)

	Range Across All Age Groups ^{1,2} (g/day)	
	Male	Female
Median	8.3 – 12.7	6.2 – 8.3
90 th Percentile	12.1 – 16.7	9.4 – 12.4

¹ Aged 9 and over

² Calculated from sodium intake (i.e., sodium intake × [m.w. sodium chloride/m.w. sodium])

If one assumes that all uses of sodium chloride in food preparation, preservation, and seasoning are amenable to substitution by Tri-Sal (1:1, w/w), then the above data may be used to estimate potential Tri-Sal intake. However, the above estimates of intake include both sodium chloride added to food and sodium naturally present in foods. Because Tri-Sal would be added to foods, it is not appropriate to base an estimate of potential intake using estimates that include sodium chloride that is both added to foods and naturally present in foods. The Institute of Medicine reports that approximately 12% of sodium in foods is naturally occurring (IOM 2005a). If estimates of potential intake of Tri-Sal are reduced by 12% to account for sodium naturally present in foods that cannot be replaced by Tri-Sal, the following intake estimates are obtained (Table 7).

**Table 7. Potential Tri-Sal Intake From Food
Assuming 100% Replacement of All Added Sodium Chloride**

	Range Across All Age Groups ^{1,2} (g/day)	
	Male	Female
Median	7.3 – 11.1	5.4 - 7.3
90 th Percentile	10.7 – 14.7	8.3 – 10.9

¹ Aged 9 and over

² Calculated from sodium intake (i.e., sodium intake × [m.w. sodium chloride/m.w. sodium])

As indicated above, only a portion of sodium chloride added to foods is expected to be replaced by Tri-Sal because of palatability issues. Assuming a maximum 50% replacement by Tri-Sal of sodium chloride added to food (1:1, w/w), the following maximum potential intakes may be estimated (Table 8):

**Table 8. Potential Tri-Sal Intake From Food
Assuming a Maximum 50% Replacement of Added Sodium Chloride**

	Range Across All Age Groups ^{1,2} (g/day)	
	Male	Female
Median	3.7 – 5.6	2.7 – 3.7
90 th Percentile	5.3 – 7.3	4.1 – 5.4

¹ Aged 9 and over

² Calculated from sodium intake (i.e., sodium intake × [m.w. sodium chloride/m.w. sodium])

4.2.1 Worst Case Intake Estimate

For a worst case estimate of potential intake of Tri-Sal, it is assumed that the maximum 90th percentile intake by males from Table 8 (7.3 g/day) is consumed by all age groups. Using the percentages of each ion present in Tri-Sal, the maximum worst case total intake of the individual ions would therefore be:

Table 9. Worst Case Intake Estimate¹

	90th Percentile Intake (mg/day)
Mg ²⁺ (9.27%)	681
NH ₄ ⁺ (5.2%)	382
K ⁺ (3.73%)	274
Cl ⁻ (40.6%)	2,982

¹ Water constitutes 41.25% of Tri-Sal.

4.2.2 Median Intake Estimate

Using intake estimates for the full range of median values for males and females from Table 8 and the percentage composition of the ions in Tri-Sal, the following estimates of intake of the individual ions that will result from use of Tri-Sal are obtained:

Table 10. Median Intake Estimates Across All Age Groups by Sex

	Intake (mg/day)	
	Men	Women
Mg ²⁺ (9.27%)	340 – 516	253 – 340
NH ₄ ⁺ (5.2%)	191 – 290	141 – 191
K ⁺ (3.73%)	137 – 208	102 – 137
Cl ⁻ (40.6%)	1,491 – 2,261	1,106 – 1,491

4.2.3 Limitations on Exposure

It is likely that both the worst case estimate of Tri-Sal intake (7.3 g/day) and the median estimates of Tri-Sal intake by males (3.7 – 5.6 g/day) and females (2.7 – 3.7 g/day) both greatly overestimate the potential daily intake. This is because a large portion (i.e., 77%) of the daily intake of sodium chloride comes from uses in food processing (IOM 2005a). Food processing uses for salt include its use for numerous technical effects other than seasoning. The technical uses for sodium chloride include preservation, enhancing food texture, binding together food components, fermentation control, and color development (Salt Institute 2008). While Tri-Sal may be useful for some technical effects for which pure sodium chloride is used, it is unlikely that all of the technical effects produced by sodium chloride will be able to be reproduced by replacing sodium chloride with Tri-Sal. Further, it is unlikely that substitution of Tri-Sal for sodium chloride will be economically feasible for many food manufacturers and consumers. Instead, it is likely that Tri-Sal will attain only a modest market share as a seasoning and preservation aid and total intakes will be less than the above estimates.

4.3 **Safety Assessment**

Tri-Sal dissolves into its component ions when exposed to aqueous media. Therefore, the evidence of safety of Tri-Sal relies in large part on the GRAS status of its ingredient salts: MgCl₂ (21 CFR 184.126), KCl (21 CFR 184.1622), and NH₄Cl (21 CFR 184.1138); each of which also dissolves into its component ions when exposed to aqueous media. All three of the individual component salts were affirmed to be GRAS by the FDA on the basis of reports prepared in the mid-1970s by the SCOGS; a group of qualified scientists who reviewed and evaluated the available exposure and safety information on each of the substances. For each of the above salts, the SCOGS Committee concluded:

"There is no evidence ... that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future (FASEB 1974, 1976, 1979)."

In addition to the FDA GRAS affirmations cited above, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established an Acceptable Daily Intake (ADI) value of "not specified" for magnesium, potassium, and ammonium chloride salts (WHO 1980, 2007). "Not specified" is a term applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect, and from its acceptable background in food does not, in the opinion of JECFA, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance.

Additional safety assessments have been prepared by panels of experts for two of the individual cations present in Tri-Sal. Upper tolerable limits of exposure have been evaluated for magnesium and potassium ions present in foods by both the U.S. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board of the Institute of Medicine (IOM 1997, 2005b) and the E.U. Scientific Committee on Foods (SCF 2006). For both magnesium and potassium consumed with the diet, no upper tolerable limit was defined (IOM 1997, 2005b, SCF 2006), indicating the safety of these ions when consumed as part of the diet.

Furthermore, the following scientific evidence is provided that demonstrates the safety of exposure according to the worst-case estimate provided above.

4.3.1 Magnesium

Intake from the diet

Estimates of the magnesium intake from the diet have tended to decline over time. During the period between 1909 and 1913, intake was estimated at approximately 408 mg/day (FNBC 1989). At approximately the time of the original SCOGS report on magnesium salts, it was estimated that the average American diet provided about 349 mg of magnesium daily (FNBC 1989). More recent estimates of daily intake of magnesium from the diet from NHANES data from 1999-2000 (i.e., 284 – 349 mg/day for adult males and 216 – 258 mg/day for adult females) demonstrate that the gradual decline in magnesium intake has continued (Ervin et al. 2004).

The current RDAs are 400 – 420 mg/day for women and 310 – 320 mg/day for men (IOM 1997). Based on NHANES III data, it was determined that among US adults, a substantial portion consume less than the RDA for magnesium (King et al. 2005; Table 11).

Table 11. Percent of Population Meeting Magnesium RDA

Magnesium Intake Group	Percent of Population
≥100 % of RDA	21.5
75% to 99% of RDA	22.6
50% to 74% of RDA	30.5
≤ 50% of RDA	25.4

Safety Assessment

Using the worst case estimate from above, it is possible that an individual may be exposed to up to an additional 681 mg/day of magnesium as a result of the use of Tri-Sal in foods. This is substantially more than the approximate 2.5 mg/day added to foods by food processors at the time of the SCOGS report (FASEB 1976). However, the higher level of intake can be concluded to be safe because the intake of Tri-Sal at this level would occur slowly over the course of the day and only in the presence of ingested food.

The primary initial symptom of excessive magnesium intake is diarrhea (IOM 1997). The laxative effect is believed to result primarily from osmotically mediated water retention in response to the presence of high concentrations of magnesium ions, which then stimulates peristalsis. At single doses of approximately 1,000 mg to 3,000 mg of magnesium, magnesium salts are marketed as laxative agents (Jafri and Pasricha 2001). Cases of transient, mild diarrhea and related symptoms of gastrointestinal distress (nausea and cramping) have been observed in some individuals after consumption of lower doses of magnesium (360 mg to 380 mg). However, diarrhea was observed when the magnesium salts were consumed as supplements in tablet, capsule, and granular forms; not when consumed with foods (IOM 1997, SCF 2001).

Similar effects are not, however, expected with Tri-Sal despite the potential consumption of up to 700 mg/day, because of the low rate of consumption of the magnesium from Tri-Sal over the course of the day. Further, the presence of food in the gastrointestinal tract coincident with the magnesium ions would be expected to counteract the osmotic gradients that underlie the laxative effects seen with pharmaceutical and dietary supplement magnesium salt products (IOM 1997). Based on a review of human study data, the National Academy of Science Institute of Medicine has determined that, "magnesium ingested as a component of food or as a food fortificant has not been reported to cause this mild, osmotic diarrhea even when large amounts are ingested (IOM 1997)." Further, the Upper Tolerable Limit for magnesium that has been established by the Institute of Medicine (350 mg/day; IOM 1997) is stated to be intended solely for supplemental magnesium (i.e., magnesium from dietary supplements) and not for magnesium in foods.

The potential for production of adverse systemic effects due to elevated levels of magnesium in the blood is limited by the body's homeostatic mechanisms. The fractional absorption of magnesium decreases with increases in intake (IOM 1997). Therefore, relatively large doses must be consumed in order for adverse systemic effects associated with hypermagnesemia to be observed. Systemic adverse effects, such as metabolic acidosis, hypokalemia, hypotension, and hypoventilation have been only after daily doses of magnesium that are >10-fold higher than the worst case estimate (IOM 1997, SCF 2006). Other serious adverse effects such as cardio-respiratory arrest have been observed only after single doses of magnesium that are more than 500-fold higher than the worst case estimate (i.e., 400 g; Fleet and Cashman 2001).

Magnesium is excreted primarily in the urine (IOM 1997). However, even patients with chronic renal impairment who are unable to excrete magnesium as successfully as individuals with normal renal function are unlikely to experience hypermagnesemia following exposure to magnesium from Tri-Sal because the increment in total daily magnesium intake is relatively small. It is only when patients with renal failure are exposed to large pharmacological doses of magnesium that hypermagnesemia is observed. For example, a study commonly cited where patients with renal failure exhibited unhealthy elevated magnesium levels after oral magnesium treatment (Randall et al. 1964) evaluated patients who were exposed to oral magnesium at total daily doses that are approximately 10 times⁸ that provided by the maximum worst case exposure estimate. Furthermore, severe renal impairment must occur before magnesium homeostasis is

⁸ Patients received oral magnesium hydroxide (30 mL) every 3 hours for a total daily dose of 180 mL. Magnesium content of 5 mL = 415 mg x (24.3/58.34) = 172.9 mg. Therefore, magnesium content of 180 mL = 172.9 mg x (180/5) = 6,224 mg.

adversely affected. The threshold limit for glomerular filtration to have an effect on magnesium homeostasis has been demonstrated to be 30 mL/min (Mordes and Wacker 1978), a level consistent with the most severe degrees of renal failure (National Kidney Foundation 2008). Thus, it is unlikely that even patients with chronic renal failure will experience adverse effects due to the comparatively small increments in daily magnesium intake provided by Tri-Sal.

Adverse effects of magnesium such as sedation in infants have also been cited as limitation to the use of magnesium in foods (WHO 2007). However, this problem is rare and typically associated with large pharmacological doses of magnesium, such as the administration of magnesium-containing antacids to low-birth-weight infants (Greer 1989). Tri-Sal is not intended for use in infant formulas. Therefore, there is no significant concern regarding adverse effects in infants resulting from possible consumption of Tri-Sal in their food.

Overall Assessment

The increment in magnesium intake by consumers as a result of the use of Tri-Sal in prepared foods and by consumers to season foods is not anticipated to produce adverse effects either locally in the gastrointestinal tract or systemically at levels likely to be consumed by even the 90th percentile consumer. Further, its use in foods would tend to increase overall magnesium intake in a population largely failing to meet recommended levels of daily magnesium intake.

4.3.2 Potassium

Intake Assessment

Large amounts of potassium are naturally present in the American diet. At the time of the SCOGS reports it was estimated that between 3.7 g/day and 7.5 g/day of potassium were provided by the average American diet (FASEB 1979). More recent estimates of intake of potassium from the NHANES surveys (NHANES 1988-1994 and NHANES 1999-2000) of food intake indicate that the median intake of potassium is somewhat lower (i.e., 2.8 g/day to 3.3 g/day for men and 2.2 g/day to 2.4 g/day for women; IOM 2004, Ervin 2004). These values are below the current level of Adequate Intake (AI) set by the IOM (4.7 g/day for both men and women; IOM 2004).

Using the worst case estimate of 90th percentile intakes from above, it is possible that an individual may be exposed to an additional 274 mg/day of potassium as a result of the use of Tri-Sal in foods. This is substantially higher than the estimated amount of potassium added to foods (i.e., 12 to 20 mg/day) at the time of the original SCOGS report. However, an additional 274 mg/day represents only an approximate 10% increase to the total daily potassium intake. When added to the potassium content of the average American diet, this additional increment is below that needed to bring levels up to those considered to be adequate.

Safety Assessment

The addition of between 200 to 300 mg/day of potassium to the diet is not expected to cause adverse effects. Such a difference is within the normal variability of daily potassium intake from the diet. The potassium content of the blood is highly regulated (even in the face of multi-gram doses of potassium; IOM 2005b). Thus, this small additional potassium intake would not be expected to be associated with any toxicity. In the original SCOGS report on potassium, the Committee considered the potential health effects of substituting potassium chloride for sodium chloride in the diet and concluded that the importance of reducing sodium intake in the diet would be greater than increased consumption of potassium (FASEB 1979). No Tolerable Upper Limit for potassium intake from foods was set by IOM (2004). When administered as a supplement to the diet, adverse gastrointestinal effects were observed only following bolus doses many-fold higher than that provided by the worst case estimate (IOM 2004; SCF 2006).

Potassium is excreted principally in the urine and the body responds rapidly to increased potassium intake with an increase in potassium excretion. Even patients with severe renal disease have been observed to be able to modulate blood levels of potassium via enhanced excretion following much larger doses of potassium than are provided by Tri-Sal (FASEB 1979). Only rare cases of hyperkalemia have been observed in patients with renal impairment following potassium salt substitute use and only at doses of potassium 10-fold or greater than that provided by the worst case estimate (IOM 2004).

Overall Assessment

The increment in potassium intake by consumers as a result of the use of Tri-Sal in prepared foods and by consumers to season foods is not anticipated to produce adverse effects at levels likely to be consumed by even the 90th percentile consumer. Further, its use in foods at the worst case (90th percentile) level of use would be insufficient to increase overall potassium intake sufficiently to meet recommended levels of daily potassium intake.

4.3.3 Ammonium

Intake Assessment

Ammonia is a natural human degradation product of protein and amino acid containing foods. Approximately 4,200 mg/day of ammonia is produced endogenously and absorbed in the gastrointestinal tract daily as a result of degradation of nitrogenous compounds in ingested food (ATSDR 2004).

Using the worst case estimate from above, it is possible that a 90th percentile consumer may be exposed to up to an additional 382 mg/day of ammonium ion as a result of the use of Tri-Sal in foods. This is approximately 5-fold greater than the amount of ammonium ion intake from ammonium salts added to foods estimated at the time of the SCOGS report (FASEB 1974). However, the additional ammonium intake would be an increase of less than 10% above the normal amount produced and absorbed daily with a normal diet.

Safety Assessment

The increase in ammonium ion consumption due to the use of Tri-Sal at the 90th percentile intake level is unlikely to exceed the daily variability in endogenous ammonium ion production and is unlikely to produce any adverse effects on health.

It has been estimated that potentially adverse effects on acid-base balance may occur in humans at levels of ingestion of around 100-150 mg of ammonium chloride per kilogram body weight per day (equivalent to 34-51 mg ammonium/kg/day; FASEB 1974, SCF 1992). This is approximately 5-fold greater than the 7.6 mg/kg/day of ammonium ion intake for a 50-kg consumer of Tri-Sal at the 90th percentile level of intake.

Further evidence for the lack of an impact of the worst case dose of ammonium ion (382 mg/day) on health comes from a study in which plasma ammonium ion levels were evaluated after individuals were given ammonium chloride in tablet form as a single dose of 20 mg per pound body weight. For a 150-pound individual, this is approximately 8 times the dose provided by the worst case estimate (Conn 1972). Of the subjects tested, only approximately half demonstrated any increase in plasma ammonium levels and that increase was small and transient. It is extremely unlikely that individuals consuming the Tri-Sal as part of the diet over the course of the day would exhibit any detectable increase in levels of ammonium ion naturally present in the blood or any adverse systemic effects from this dose.

Overall Assessment

The increment in ammonium intake by consumers as a result of the use of Tri-Sal in prepared foods and by consumers to season foods is not anticipated to produce adverse effects at levels likely to be consumed by even the 90th percentile consumer.

4.4 Overall Safety Conclusion

Both in the individual SCOGS reports and the subsequent reports by expert panels on the safety of the component salts used in the manufacture of Tri-Sal, it has been concluded that levels of exposure to the ions in Tri-Sal by even the 90th percentile consumer would reasonably be expected to be safe. This worst-case estimate for exposure to Tri-Sal provides negligible impact on the daily human exposure through the diet to either potassium or ammonium ions and therefore can be concluded to yield negligible impact on human health. Under the conditions of the worst-case exposure, daily magnesium ion intake may be expected to approximately double. However, this doubling is not expected to produce any adverse effects on health as exposures would: (1) be distributed over the course of the day, and (2) would occur only in conjunction with food intake. Under these conditions of exposure, no adverse health effects have been demonstrated.

Based on the anticipation that no adverse health effects are likely, even with complete substitution of up to 50% of the sodium chloride consumed by individuals with high levels of salt

intake (i.e., the 90th percentile consumer), it is safe to assume that the actual levels of exposure with a more modest market share would also be expected to be safe. Further, large segments of the general U.S. population have in recent dietary surveys demonstrated intake levels of magnesium and potassium intake below those recommended by recognized experts to maintain good health. Thus, additional intake of Tri-Sal as a replacement for a portion of sodium chloride in the diet may have beneficial effects.

5.0 IMPACT ON FOOD STANDARDS

Salt (i.e., sodium chloride) is a required or optional ingredient in many standardized foods and meat products. However, with limited exceptions,⁹ these standardized foods do not require a specific amount of salt. Therefore, there is flexibility for food manufacturers to adjust food formulations and lower sodium chloride content. Tri-Sal could be added to foods as a flavoring agent in place of a portion of the usual salt added. Tri-Sal content would be limited by individual food manufacturers to the extent that technical effects based on the presence of sodium chloride in the foods are not compromised by the lower sodium chloride content.

⁹ Country Ham, Country Style Ham, Dry Cured Ham, Country Pork Shoulder, Country Style Pork Shoulder, and Dry Cured Pork Shoulder have required minimum levels of internal salt content (at least 4%) and use of salt to produce a brine (of not less than 10% if nitrates are not used in its production) (9 CFR 319.106). Italian style, Serrano, and Iberian hams and Iberian pork shoulder require a salt coating during preparation (9 CFR 94.17). Salt whole egg and salt yolk products specify a minimum amount of salt (9 CFR 590).

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Carlson, Susan

From: Carrie Rabe [Carrie.Rabe@weinberggroup.com]
Sent: Wednesday, December 17, 2008 1:56 PM
To: Carlson, Susan
Subject: RE: Suggested changes to GRAS Notification

Attachments: GRAS Exemption Claim (replacement page 3) 12-17-08.pdf; GRAS Exemption Claim (replacement page 4) 12-17-08.pdf



GRAS Exemption Claim (replacem...



GRAS Exemption Claim (replacem...

Hello Susan,

I am attaching the replacement pages. Please do not hesitate to contact me if there is anything else that you need.

Carrie Rabe, Ph.D.
Senior Consultant, Pharmaceuticals
THE WEINBERG GROUP INC.
1220 Nineteenth St., N.W., Suite 300
Washington, DC 20036

Phone: 202.833.8077
Fax: 202.833.7057

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>>> "Carlson, Susan" <Susan.Carlson@fda.hhs.gov> 12/17/2008 10:49 AM >>>
Hello Carrie,

This is fine. Please e-mail me replacement pages as Adobe Acrobat files (like you did for the complete notice). For the purposes of our program, our receipt date for the notice will be the date we receive the replacement pages (which complete the notice and make it "file able.")

Thank you!
--Susan

-----Original Message-----

From: Carrie Rabe [mailto:Carrie.Rabe@weinberggroup.com]
Sent: Tuesday, December 16, 2008 3:21 PM
To: Carlson, Susan
Cc: Kara Wilhelm
Subject: Suggested changes to GRAS Notification

Hi Susan,

Here are the revisions of the two phrases that needed rewriting:

Smart Salt Inc. has determined that Tri-Sal is generally recognized as safe (GRAS) based on scientific procedures and, therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below.

and

All data and information that was used as a basis for this GRAS determination can be provided to the Food and Drug Administration (FDA) upon request and is also available for the FDA's copying and review, by contacting Tapio Maki.

Please let me know about the need to change the submission date as well.

All the best,

Carrie

1.0 GRAS EXEMPTION CLAIM AND OVERVIEW

1.1 Claim of Exemption from the Requirement for Premarket Approval

Smart Salt Inc. has determined that Tri-Sal is generally recognized as safe (GRAS) based on scientific procedures and, therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Tapio Maki
CEO
Smart Salt, Inc.
1261 Prospect Street
Suite 9
La Jolla, CA 92037

December 5, 2008
Date

RECEIVED
DEC 17 2008

BY:

1.2 Name and Address of the Notifier

Tapio Maki
CEO
Smart Salt, Inc.
1261 Prospect Street
Suite 9
La Jolla, CA 92037

Telephone: 858.456.2437
Fax: 858.456.2239
Email: tapio.maki@smartsalt.com

1.3 Common Name of the Notified Substance

The common name for the triple salt that is the subject of this notification is Tri-Sal.

1.4 Conditions of Use

Tri-Sal is intended to be used as a substitute for a portion of the sodium chloride used in foods. The purpose of the product is to lower sodium intake. Tri-Sal will be used in food in general, including meat, poultry, and egg products, but excluding infant formula.

1.5 Basis of GRAS Determination

Pursuant to 21 CFR 170.3, Tri-Sal has been determined to be GRAS by scientific procedures for its intended conditions of use. The safety of Tri-Sal is supported by the fact that the triple salt readily dissolves in aqueous media into the same constituent ions as the component salts that are used in its manufacture. Each of the component salts has been affirmed as GRAS by the US Food and Drug Administration: 21 CFR 184.1138, 184.1426, and 184.1622 for ammonium chloride, magnesium chloride, and potassium chloride, respectively, based on reviews by the Select Committee on GRAS Substances. Ammonium chloride is affirmed as GRAS as a "flavor enhancer," magnesium chloride as a "flavoring agent," and potassium chloride as both a "flavor enhancer" and "flavoring agent."

1.6 Availability of Information

All data and information that was used as a basis for this GRAS determination can be provided to the Food and Drug Administration (FDA) upon request and is also available for the FDA's copying and review, by contacting Tapio Maki.

SUBMISSION END

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