April 28, 2014

Office of Food Additive Safety
Division of Biotechnology and GRAS Notice Review, (HFS-255)
Center for Food safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

To whom it may concern,

In accordance with the 21 CFR 170.36 (62 FR18937; April 17, 1997), MitoGene Beverage Company, LLC hereby provides notice of a claim that the use of **molecular hydrogen** (H_2) solubilized in water is generally recognized as safe (GRAS) and therefore exempt from the premarket approval requirement of the Federal Food, Drug and Cosmetic Act. Based upon scientific data and information, including that in the attached documents, MitoGene Beverage Company has determined, that molecular hydrogen solubilized in water is general recognized as safe. The data and information that are the basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at reasonable times at the address specified below in the "Information About the Notifier" section, or will be sent to the FDA upon request. As required, three copies of the notification, including supporting documentation, are provided.

If you have any questions regarding this notification, please feel free to contact any one of the submitters listed here. Thank you very much for your time and consideration.

Sincerely,

(b) (6)

04/28/2014

Dr. Cody C. Cook, Ph.D., M.D.
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Apr. 28, 2014

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Enclosures

Information About The Notifier

MitoGene Beverage Company, LLC
Cody Cook (Manager)
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OR:
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Alexander, Arkansas 72002

Intended Use

This GRAS notification serves to delineate the intended use of molecular hydrogen up to a concentration of 2.14% (vol $H_{2\,(gas)}$/vol $H_2O_{\,(liq)}$) (saturation) in pure drinking water, flavored beverages, and soda drinks for the purpose of preventing oxidation to the beverages, beverage containers, and the consumer.

Identity of Notified Substance

Hydrogen Gas

Synonyms for hydrogen include dihydrogen, ortho-hydrogen/para-hydrogen, and most commonly, molecular hydrogen. Hydrogen has an empirical formula of H, and a structural formula of H_2. The CAS number of hydrogen is 1333-74-0.

Molecular weight: 2.016 g/mol
Specific volume (1.013 bar and 21 °C, 70 °F): 11.986 m^3/kg
Solubility in water (1.013 bar and 0 °C, 32 °F): 0.0214 mL $H_{2\,(gas)}$/mL $H_2O_{\,(liq)}$
Concentration in air: 0.00005% (vol)

Description of Hydrogen Gas: Hydrogen is a non-toxic, flammable, lighter than air gas, which reacts with oxidizing compounds. In terms of environmental and human health, the main risk of hydrogen exposure is due to its flammability; the gas is flammable in air between 4-75% by volume. The set exposure limits to hydrogen are 100% by volume due to oxygen depletion by simple asphyxiation. As a cryogenic fluid, hydrogen exposure can cause frostbite.

According to manufacturer material safety data sheets (MSDS), and a wealth of scientific literature, hydrogen has no known acute or chronic toxicity, carcinogenic effects, mutagenic effects, or reproductive toxicity. When dissolved in water, hydrogen has a rating of 0/0/0 for health/flammability/instability on the Hazardous Material Information System (U.S.A) indicating that it represents no significant risk toward human health, is not flammable, and is chemically stable.

Method of manufacture

Manufacturing of Hydrogen Gas: Food grade molecular hydrogen gas, according to the intended application, is produced industrially through steam reformation of natural gas (NexAir). Trace contaminants include oxygen (O_2), water vapor (H_2O), total hydrocarbon (THC), argon (Ar), carbon monoxide (CO), carbon dioxide (CO_2), and nitrogen (N_2). None of the trace contaminants are toxic at the specified levels or in the intended use.

Specifications – Good Manufacturing Practices

Food grade hydrogen should be High Purity (99.995%) or greater. To establish acceptable contaminant levels in food grade hydrogen for good manufacturing practices, the company has assessed the currently accepted limits of similarly used food grade gases, e.g., carbon dioxide and nitrogen. Based on these data (Figures 3, 4), we have established levels for food grade hydrogen (Figure 2). All executions of the described intended use in this notification will follow these good manufacturing practices.

Applicable Conditions of Use

The chemical properties of hydrogen make it ideally suited for several applications within the food and beverage industry. Molecular hydrogen is non-toxic and is a potent antioxidant, making it a valuable preservative. The current intended application is the use of solubilized H_2 in pure drinking water, flavored beverages, and soda drinks. The presence of H_2 in such beverages serves as an antioxidant and protecting the beverage and beverage delivery system (i.e. the can) from oxidation.

Hydrogen (H_2)-enriched beverages (including drinking water, flavored water, and soft-drinks), are produced by introducing high purity (99.995%) hydrogen gas into purified drinking water under high-pressure (~ 100 psi), loosely analogous to the carbonation process for carbonated beverages. This process solubilizes hydrogen gas at the saturation limit of water. Due to the chemical solubility of hydrogen in water, the concentration in such beverages reaches up to 0.0214 mL $H_{2\,(gas)}$/mL $H_2O_{\,(liq)}$. In contrast, carbonated beverages may contain up to 1.72 mL $CO_{2\,(gas)}$/mL $H_2O_{\,(liq)}$. The resulting product contains hydrogen at a concentration well below the lower flammability limit. In this form, dissolved hydrogen is completely non-toxic, and non-flammable.

Because of hydrogen's biological safety profile, hydrogen-enriched beverages are suitable for persons of all ages and medical conditions under the described application conditions (consumption of up to 2 L/day of 0.0214 mL $H_{2\,gas}$/mL H_2O). As of this date, there is no evidence in the scientific literature that H_2-enriched beverages should not be consumed by any segment of the population.

Self-limiting Levels of Use

The solubilization of H_2 in a beverage limits the access of the molecule to oxygen such that it is non-flammable in a liquid medium. Due to the chemical solubility of hydrogen in water (Figure 1), hydrogen may reach a maximum concentration of 0.0214 mL $H_{2\,gas}$/mL $H_2O_{\,(liq)}$, corresponding to 1.8 ppm. This concentration of H_2 in water is well below the lower flammability limit of molecular hydrogen (4% $H_{2\,(gas)}$) in air and can't be concentrated further. Upon exposure to the air, the dissolved hydrogen slowly diffuses out of solution (with a half-life of ~2 hours) and

into the air, becoming more dilute. Notably, hydrogen is naturally present in air at 0.000055% (v/v).

Dietary Exposure

Assuming a maximum consumption of 2 L hydrogen enriched beverages per day, total hydrogen exposure is equal to 3.2 mg of hydrogen. Given that the only health risk of hydrogen exposure is due to suffocation, these consumption levels are generally regarded as safe by scientists, clinicians, and as verified through scientific proceedings.

History of Use: Hydrogen as an Antioxidant/Food Preservative

The international community recognizes the value of hydrogen as a food preservative, antioxidant, and packaging leak indicator. Molecular hydrogen is used in the European Union, under the category of a packaging gas E949 (http://www.food.gov.uk/policy-advice/additivesbranch/enumberlist#h_7). In this context, liquids and food stuffs are exposed to and stored in the presence of H_2 gas for long periods of time, whereby hydrogen diffuses through and permeates the product. Hydrogen becomes absorbed such that it protects the product and/or container from oxidative degradation. Hydrogen gas is ideal for these purposes because of its large specific volume, low molecular weight, and non-toxic profile.

Comprehensive Discussion of the Scientific Proceedings used for the GRAS Determination

The determination that animal and human consumption of H_2 in beverages is GRAS is based on scientific data, information, methods, and principles that have been collected from the publically available scientific literature. Reports of the consumption of H_2 in animal and human studies are unanimous in the standing that H_2 is GRAS. The reports have been extensively published in primary, peer-reviewed scientific journals of the highest tier (Dole, Wilson et al. 1975; Ohsawa, Ishikawa et al. 2007), and supported by the secondary scientific literature such as scientific review articles (Wood and Gladwin 2007). The consumption of H_2 saturated water has been extensively studied (Shirahata, Kabayama et al. 1997; Kim and Kim 2006). Electrolyzed-reduced water is characterized with a highly negative redox potential, in addition to, high dissolved H_2 content. Consumption of hydrogen-enriched water has been extensively studied (Kajiyama, Hasegawa et al. 2008; Ohsawa, Nishimaki et al. 2008; Sato, Kajiyama et al. 2008; Fu, Ito et al. 2009; Fujita, Seike et al. 2009; Kajiya, Silva et al. 2009; Nagata, Nakashima-Kamimura et al. 2009; Nakashima-Kamimura, Mori et al. 2009; Cardinal, Zhan et al. 2010; Liu, Liu et al. 2011). The consumption of H_2 has been assessed across a variety of disease models and many research contexts including; oxidative stress markers, glucose metabolism, diabetes, inflammatory bowel disease, and pathogenic events (Kamimura, Nishimaki et al. 2011., Kajiyama, Hasegawa et al. 2008; Nakao, Toyoda et al. 2010., Kajiya, Silva et al. 2009; Nakashima-Kamimura, Mori et al. 2009).

Disposition of Molecular Hydrogen in Humans

The pharmacokinetic properties of hydrogen-enriched beverages have been evaluated by the medical and scientific communities over decades of research in many fields of study. The

following data review and highlight key scientific studies demonstrating the scientific consensus that the intended application described in this document is generally regarded as safe.

Absorption

After consuming H_2-enriched beverages, H_2 is rapidly and completely absorbed in healthy adult volunteers that have fasted, as determined by hydrogen breath tests. The concentration of H_2 in exhaled breath reaches a peak (35-to-56.8 ± 27.8 ppm) at 15 minutes in a dose-dependent manner (Kajiyama, Hasegawa et al. 2008; Shimouchi, Nose et al. 2009). H_2 reaches peak absorption within ~15 minutes following oral consumption (Cardinal, Zhan et al. 2010). It is generally reported that acute ingestion of H_2-enriched water rapidly increases the H_2 partial pressure in the alimentary tract, and sub-mucosal alimentary vessels. Kajiya et al. and others have reported that the concentration of H_2 in the stomach of animal models, that were directly administered H_2-enriched water by catheter, increased within 5 minutes (503.8 ± 160.3 μM, 1.0 ppm) until the concentration began to decrease by 10 minutes (200.8 ± 106.6 μM, 0.40 ppm) and return to baseline levels within one hour (Kajiya, Silva et al. 2009). The same report noted that the concentration of H_2 in the colon gradually increased to its highest level (88.0 ± 26.5 μM, 0.18 ppm) at 30 minutes, presumably by a combination of cross-epithelial diffusion (Lemke, van Alen et al. 2001) and the vascular-based transport processes (Bond, Levitt et al. 1975), until 50 minutes, when the concentration of H_2 returned to the exogenous baseline levels already present in the colon (58.0 ± 15.1 μM, 0.12 ppm) (Kajiya, Silva et al. 2009). Nagata et al. has reported that the incorporation of (0.8 mM, 1.6 ppm) hydrogen-enriched water directly into the stomach of a rat (3.5 mL per 230 g, 15 mL/kg) increased the H_2 concentration in blood within 3 minutes (Nagata, Nakashima-Kamimura et al. 2009), while a similar study has reported that the concentration of H_2 in the blood is increased by 3.7-fold and 7.6-fold in the fed and fasted state (Nakashima-Kamimura, Mori et al. 2009). It should also be noted that hydrogen gas has been administered to animals and humans through intraperitoneal injection, intravenous injection, and via eye drops with similar results to oral consumption (Mao, Zheng et al. 2009; Nakayama, Kabayama et al. 2009; Zheng, Mao et al. 2009; Oharazawa, Igarashi et al. 2010; Zheng, Liu et al. 2010; Chen, Sun et al. 2011; Ji, Hui et al. 2011).

Distribution

H_2 is electronically neutral and is much smaller than molecular oxygen (O_2). These properties allow H_2 to penetrate the cellular and intracellular membranes of cells and organelles explaining its large volume of distribution. The highly diffusible and lipid soluble nature of H_2 enables it to reach equilibrium nearly instantly with respect to blood and tissue. This fast diffusion results in H_2 being distributed to tissues in proportion to the regional blood flow of the tissue. These properties have been exploited in the clinic, making H_2 a powerful tool for measuring arterial and venous blood flow (Aukland, Bower et al. 1964). When consumed orally via enriched beverages, H_2 is distributed throughout the total volume of water in the body. Currently there are still technical challenges in detecting low levels of H_2 within tissues (Fujita, Seike et al. 2009). During the distribution phase, H_2 is diluted by 160 fold between the stomach and blood (Nagata, Nakashima-Kamimura et al. 2009). There is an even greater expected dilution factor between the blood and tissue, suggesting that the concentration of H_2 in distal tissues is below the detection limit of even the most sensitive analytical methods currently available. In chronic

exposure studies (60 days), the level of H_2 in the circulation of animals is comparable to that of naive animals (Cardinal, Zhan et al. 2010). These results confirm that H_2 does not accumulate in the body after consumption of H_2-enriched beverages. Further, the pharmacokinetic parameters did not change during the course of the study.

Metabolism

The metabolism of H_2 is important from both anabolic and catabolic perspectives. H_2 is a natural component of abdominal gas (Hammer 1993) where it is reportedly catabolized by colonic microflora into still unconfirmed metabolites such as methane (Christl, Murgatroyd et al. 1992). Endogenous H_2 is also generated through anabolic pathways carried out exclusively by numerous strains of colonic microflora (Reth 2002). Fermentation is also increased in response to a diet of numerous foods with un-absorbable carbohydrates, such as milk, commercial dietary fiber, soybean flour, and oligofructose in a number of vegetables, fruits, and whole grains (O'Brien, Thompson et al. 1987; Kondo and Nakae 1996; Suarez, Springfield et al. 1999; Cherbut 2002; Shimouchi, Nose et al. 2009). For example, the ingestion of milk exhibits a delayed and sustained increase of breath hydrogen (164 ppm) in subjects with hypolactasia for up to 540 minutes, in comparison to the relative (60 min) transient increase in hydrogen (2-to-55 ppm) that is noted with H_2-enriched water (Kajiyama, Hasegawa et al. 2008; Nagata, Nakashima-Kamimura et al. 2009; Shimouchi, Nose et al. 2009).

Excretion/Elimination

Following absorption via oral consumption, the concentration of H_2 in the blood decreases to baseline levels (11.2 ± 6.5 ppm) within 2.5 hours (Kajiyama, Hasegawa et al. 2008). The major route of H_2 elimination is through the respiratory system due to the low rate of metabolism, and high volatility of the compound (Shimouchi, Nose et al. 2009). The vapor-liquid equilibrium constant for H_2 drives hydrogen into the vapor phase, facilitating gas exchange of H_2 from the blood to the alveolar ducts. Once in the gas phase, hydrogen is uni-directionally expelled from the body upon exhalation due to the ~40,000-fold difference in concentration of H_2 between the blood and the atmosphere.

(III). Safety Profile of the Consumption of H_2: The safety profile of the consumption of H_2 is a reflection of the well-defined characteristics of the properties of the gas with respect to the human body. The role of H_2 in the body has been studied extensively (Ohsawa, Ishikawa et al. 2007; Fujita, Seike et al. 2009)(Sato, Kajiyama et al. 2008)(Bjelakovic, Nikolova et al. 2007; Ohsawa, Ishikawa et al. 2007; Wood and Gladwin 2007). Throughout the myriad animal models and human studies which have exploited hydrogen consumption, either as an non-flammable gas (<4%) or in H_2-enriched water (< 0.8 mM, 1.6 ppm), there are no reports to-date of any toxicity or deleterious changes in physiological parameters (e.g., body temperature, heart rate) associated with administration of H_2. (Ohsawa, Ishikawa et al. 2007; Hayashida, Sano et al. 2008; Kajiyama, Hasegawa et al. 2008; Ji, Liu et al. 2010; Nakao, Toyoda et al. 2010; Xie, Yu et al. 2010; Xie, Yu et al. 2010; Huang, Xie et al. 2011). It is important to note that the short-term and long-term consumption of H_2 in animal and human studies has been evaluated in animal models and human studies that are subjected to a wide variety of (patho)physiologies of organ

damage, and multiple-organ damage. The lack of negative interactions with the consumption of H_2 in these models of poor health further demonstrates that H_2 is Generally Regarded As Safe.

The safety profile for the human consumption of H_2 has been further supported with 17 year-long studies on cells, mice, monkeys, and deep sea divers (COMEX HYDRA program, Marseille). Extremely high concentrations of H_2 (49%) have been utilized in hydreliox for very deep technical diving ventures to shorten decompression time, prevent decompression sickness, avert nitrogen narcosis, and reduce airway pressure (Abraini, Gardette-Chauffour et al. 1994). The hydreoliox mixture consisted of hydrogen, helium and oxygen at relative concentrations of 49% H_2, 50% $He_{2\,(gas)}$ and 1% $O_{2\,(gas)}$, respectively. The absorption of H_2 in these extremely high concentrations has not been associated with toxic effects, including no reports of intestinal motility changes (Lafay, Barthelemy et al. 1995; Fontanari, Badier et al. 2000). The high concentration of H_2 that has been utilized in inhalation and diver studies suggest that 16 mM in blood could be safe (Fontanari, Badier et al. 2000), confirming that the concentrations reached with the consumption of H_2 in beverages is GRAS.

Moreover, endogenous breath hydrogen levels fluctuate markedly during daily life, ranging from several ppm to 50 ppm or more (Sone, Tanida et al. 2000). The concentration of H_2 in the circulation of humans is enhanced by exercise, physical stress, and mental stress (Kondo and Nakae 1996; Suarez, Springfield et al. 1999). Thus, the hydrogen-producing capability of H_2-enriched water is within the range of H_2 that is produced when people with hypolactasia consume milk.

Scientific Conclusion that Hydrogen-Enriched Beverages are GRAS: The collective review of the scientific literature shows a unanimous acknowledgment that H_2, one of the most well understood molecules, is a generally recognized as safe alternative to the commercialized antioxidants in beverages based on the premise that the gas is easily available in pure form and without toxicity. Overall, no toxicity of any kind has been attributed to the *ad libitum* consumption of H_2 in the diet. Similarly, no contradictions have been noted with any other chemically or pharmacologically related or non-related substance in the diet of animals or humans. The scientific literature is devoid of any report of investigations or other information that may appear to be inconsistent with the MitoGene, LLC self-determination that above described intended use of hydrogen is GRAS.

Signatures

(b) (6)

04/28/2014

Cody C. Cook, Ph.D., M.D.
Manager, MitoGene Beverage Company, LLC

(b) (6)

Apr 28, 2014

Drew R. Jones, Ph.D.
Manager, MitoGene Beverage Company, LLC

Figures

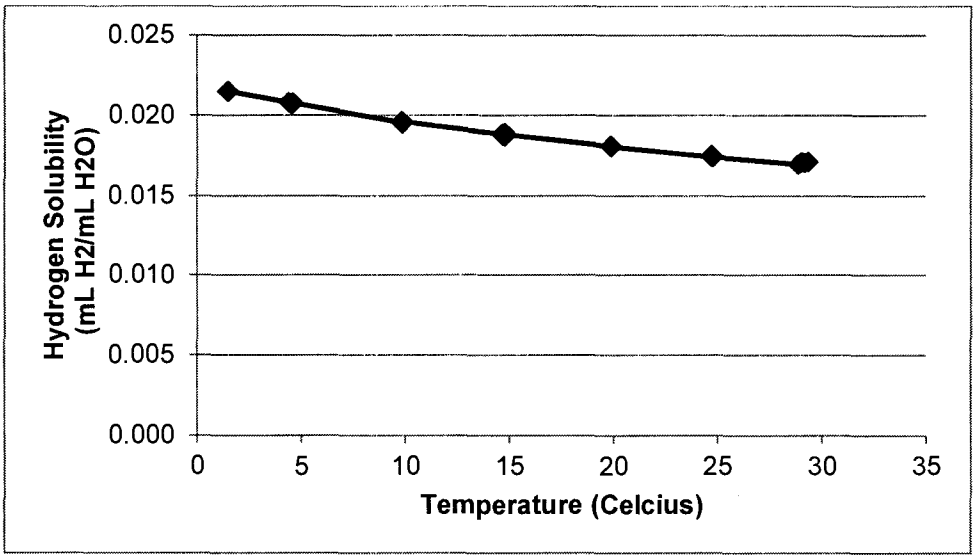

Figure 1: Solubility of Hydrogen Gas in Degassed, Distilled Water. Data adapted from (Thomas E. Crozier 1974).

nexAir

Gas Technologies
Medical Technologies
Safety Technologies
Welding Technologies

January 2, 2013

Dear Customer:

This is your Certificate of Analysis:

Product: Hydrogen

Sample Serial Number: (b) (6)

Lot Number: (b) (6)

Component	Min Purity	Analytical Results	Analytical Method
Oxygen	<1.0 ppm	<1.0 ppm	Electrochemical Cell (Delta F)
Moisture	<3.0 ppm	<2.0 ppm	Meeco
Total Hydrocarbons	<0.5 ppm	<0.5 ppm	THC Analyzer
Nitrogen	<6.0 ppm	< 6.0 ppm	GC-TCD
Assay		> 99.999%	

(b) (6)

Jason Spires
Lab Analyst

nexAir, LLC · 1259 N McLean Blvd · Memphis, TN 38108 · (901) 729-5540 · (800) 294-8062 · (901) 729-5575 fax · www.nexair.com

Figure 2: Certificate of Analysis for Food Grade Hydrogen

PRAXAIR

November 19, 2013

nexAir
PO Box 161182
Memphis, TN 38116

Praxair # 8512262

Dear Customer,

This is to advise you that liquid Carbon Dioxide supplied by Praxair, Inc. to your facility at 1211 North McLean Blvd, Memphis, TN 38108 meets or exceeds the Food Grade specifications as follows:

Minimum Assay: 99.8%	Total Sulfur: 0.5 ppm
Acetaldehyde: 0.5 ppm	Total Hydrocarbon content (as methane) : 50 ppm
Carbon Monoxide: 10 ppm	Hydrogen Sulfide: 0.5 ppm
Carbonyl Sulfide: 0.5 ppm	Non-Volatile Residue: 10 ppm
Nitric Oxide + Nitrogen Dioxide: 5 ppm	Odor/Taste: Free of foreign odor or taste
Oxygen: 50 ppm	Moisture: 20 ppm
Sulfur Dioxide: 5 ppm	

The CGA lists the typical use for this grade of product as food processing. Carbon Dioxide is listed in the Code of Federal Regulations 21 CFR 184.1240 as Generally Recognized as Safe (GRAS) as a direct human food ingredient (see attached).

Sincerely,

Tim Lowry
Praxair, Inc
Senior Account Manager

Figure 3: Reference Ranges of Contaminants for Food Grade Carbon Dioxide

PRAXAIR

April 11, 2013

nexAir, LLC
PO Box 161182
Memphis, TN 38186

Praxair # 8507527

Dear Customer:

This is to advise you that the liquid nitrogen supplied by Praxair, Inc. delivered to nexAir at 1211 N McLean Blvd, Memphis, TN 38108 has a purity guarantee of 99.998% by difference and meets or exceeds the following specifications:

COMPONENT	SPECIFICATION
Oxygen	8.0 PPM
Moisture	4.0 PPM
Carbon Monoxide	10.0 PPM
Odor	None detected

Nitrogen is listed in the Code of Federal Regulations 21 CFR 184.1540 as Generally Recognized as Safe (GRAS) as a direct human food ingredient. See attached. Also, the Compressed Gas Association lists typical uses for this grade of product as general industrial usage, process gases, inerting, food, and heat treatment applications.

Sincerely,

(b) (6)

Tim Lowry
Praxair, Inc.
NAIG Senior Account Manager

Page 1 of 2

Figure 4: Reference Ranges of Contaminants for Food Grade Nitrogen

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