June 9, 2021

Lowell Marshall
Electronic Submissions Gateway
U.S. Food and Drug Administration
3WFN, Room 7C34
12225 Wilkins Avenue
Rockville, MD 20852

RE: ToxStrategies, Inc., Representation of Cargill, Incorporated

Dear Sir/Madam:

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, please accept this Authorization Letter. This letter is to certify that Cargill, Incorporated, ("Cargill"), with its primary offices located at 15407 McGinty Rd. Wayzata, MN 5539, authorizes ToxStrategies, Inc., with primary offices located at 23501 Cinco Ranch Blvd., Suite B226, Katy, Texas 77494, to submit in the Electronic Submissions Gateway on behalf of Cargill.

Sincerely,

Tony Pavel
Senior Food Lawyer
Global Food Law Team Lead

TP:kp

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GRAS Determination of Carbon Monoxide for Use in Modified Atmosphere Packaging for Fully Cooked, Pre-Packed, Ready-to-Eat, Deli Meats

JUNE 10, 2021

ToxStrategies

Innovative solutions
Sound science

GRAS Determination of Carbon Monoxide for Use in Modified Atmosphere Packaging for Fully Cooked, Pre-Packed, Ready-to-Eat Deli Meats

SUBMITTED BY:

Cargill, Inc.
15407 McGinty Road
Wayzata, MN 55391

SUBMITTED TO:

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
HFS-200
5100 Paint Branch Parkway
College Park MD 20740-3835

CONTACT FOR TECHNICAL OR OTHER INFORMATION

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June 10, 2021

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Acronyms

ACGIH	American Conference for Governmental Industrial Hygienists
ADI	acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CO	carbon monoxide
CO_2	carbon dioxide
COHb	carboxyhemoglobin
EPA	US Environmental Protection Agency
FDA	US Food and Drug Administration
GRAS	Generally Recognized as Safe
GRN	GRAS Notification
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MAP	modified atmosphere packaging
MRL	minimal risk level
NAAQS	US National Ambient Air Quality Standard
NIOSH	National Institute for Occupational Safety and Health
OSHA	US Occupational Safety and Health Administration
RTE	ready to eat
SCF	Scientific Committee on Food
TWA	time-weighted average
USDA	US Department of Agriculture

§ 170.225 Part 1, GRAS Notice: Signed Statements and Certification

(1) GRAS Notice Submission

Cargill, Incorporated (Cargill), through its agent, ToxStrategies, Inc., hereby notifies the U.S. Food and Drug Administration (FDA) of the submission of a Generally Recognized as Safe (GRAS) notice for the use of carbon monoxide (CO) in modified atmosphere packaging (MAP) for case-ready cooked meats (including but not limited to beef, pork, and poultry), in accordance with Subpart E of 21 CFR § 170.

(2) Name and Address

Cargill, Incorporated
15407 McGinty Road
Wayzata, MN 55391

(3) Name of Notified Substance

The name of the substance that is the subject of this GRAS determination is carbon monoxide (CO).

(4) Intended Use in Food

Carbon monoxide is intended for use as a component of a modified atmosphere packaging system for fully cooked, sliced, pre-packed, ready-to-eat (RTE) deli meats and poultry. As in GRAS Notification 143, carbon monoxide will be used at a target concentration of 0.4% or less (with a process tolerance of 20% in the modified environment, for a CO concentration of up to 0.48%). CO will be used in a mixture of nitrogen (0–100%) and carbon dioxide (0%–100%).

(5) Statutory Basis for GRAS Determination

Cargill, through its agent ToxStrategies, Inc., hereby notifies FDA of the submission of a GRAS notice for CO, which meets the specifications described herein and has been determined to be GRAS through scientific procedures in accordance with §170.30(a) and (b).

(6) Premarket Approval Statement

Cargill further asserts that the use of CO in food, as described below, is exempt from the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act, based on a conclusion that the notified substance is GRAS under the conditions of its intended use.

(7) Availability of Information

The data and information that serve as the basis for this GRAS determination, as well any information that has become available since the GRAS determination, will be sent to the FDA on request and are also available for the FDA's review and/or copying during customary business hours, from ToxStrategies, Inc., Naperville, IL.

(8) Data and Information Confidentiality Statement

None of the data and information in the GRAS notice is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

(9) GRAS Notice Certification

To the best of our knowledge, the GRAS notice is a complete, representative, and balanced submission. Cargill is not aware of any information that would be inconsistent with a finding that the proposed use of CO in food, that meets appropriate specifications and is used according to current Good Manufacturing Practice (cGMP), is GRAS. In addition, recent reviews of the scientific literature indicated no concerns for potential adverse health effects.

(10) Name/Position of Notifier

_____ _____

Donald F. Schmitt, M.P.H.
Senior Managing Scientist
ToxStrategies, Inc.
Agent for Cargill

Date

(11) FSIS Statement

As described above, CO will be used in fully cooked, sliced, pre-packed, RTE deli meats (including but not limited to beef, pork, and poultry) in a MAP system in a fashion similar to that described in GRAS Notification (GRN) 143, which proposed the same use in fresh beef and pork, as opposed to cooked meats, as discussed in this GRAS notice.

§ 170.230 Part 2, Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

A. Identity

Carbon monoxide is a colorless, odorless gas that has a density slightly less than air.

B. Common or Chemical Names

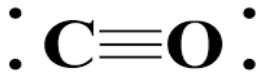
Carbon monoxide.

C. Chemical Abstracts Service (CAS) Registry Number

The CAS number for CO is 630-08-0.

D. Empirical and Structural Formula

The empirical formula for carbon monoxide is CO. The structural formula is



E. Physical/Chemical Properties

Table 1. Carbon monoxide physical/chemical properties

Property	**Carbon monoxide**
Molecular weight	28.01
Color	Colorless
Melting point	–205°C
Boiling point	–191.5°C
Density at 25°C	1.145 /L at 25°C and 1 atm[3]
Odor	Odorless
Solubility in water at 20°C	2.3 mL/100mL
Specific gravity relative to air	0.967
Critical point	140.2°C at 34.5 atm (3.5 MPa)

E. Manufacturing Process

The following narrative and flow diagram describe the typical manufacturing process for carbon monoxide.

Carbon monoxide can be produced by use of a steam methane reformer. Sulfur-free hydrocarbons such as methane, along with superheated steam, are passed over a refractory nickel catalyst placed in Ni-Cr alloy tubes. The hydrocarbon/steam mixture then converts to hydrogen and carbon oxides. The following chemical reactions are excerpted from GRN 143.

$$C_nH_m + nH_2O \Leftrightarrow (n + m/2)\, H_2 + nCO \qquad (1)$$

$$CH_4 + H_2O \Leftrightarrow CO + 3H_2 \qquad (2)$$

$$CO + H_2O \Leftrightarrow CO_2 + H_2 \qquad (3)$$

The process ultimately produces hydrogen, CO_2, CO, methane, and steam. The CO and hydrogen components are then separated from each other by techniques that include cryogenic separation.

Product Specifications

The CO used in the MAP system will be of food-grade quality and calls for a minimum CO content of 98%, the same as the specifications put forth in GRN 143. Any impurities present would consist of components found in the atmosphere, such as N_2, O_2, CO_2, argon, H_2O, H_2, and/or CH_4.

Conditions of Use

The proposed use of the MAP system containing CO with cooked meats is identical to that described in GRN 143 (part III) for fresh meat products. The use of CO is meant only to stabilize the color of the meat and does not affect microbial growth. The proposed system is not intended to extend the shelf life of cooked meat products beyond the shelf lives already established for similar MAP systems.

A study of the shelf life of cooked beef in the proposed MAP over a 70-day period was conducted by Cargill, and the report results can be found in Appendix A. The indicators of spoilage (odor, aerobic plate count growth, lactic acid bacteria growth) were similar for both control and CO treatments, regardless of the color of the product.

§ 170.235 Part 3, Dietary Exposure

Proposed Uses

Carbon monoxide is intended for use as a component of a modified atmosphere packaging (MAP) system for fully cooked, sliced, pre-packed, ready-to-eat (RTE) deli meats and poultry. As in GRAS Notification 143, carbon monoxide will be used at a target concentration of 0.4% or less (with a process tolerance of 20% in the modified environment, for a CO concentration of up to 0.48%). CO will be used in a mixture of nitrogen (0–100%) and carbon dioxide (0%–100%).

GRN 143 (FDA, 2004a) was a GRAS notification from Precept Foods, LLC (Cargill Joint Venture) for the use of a MAP system using a target concentration of 0.4% CO in case-ready fresh meat (beef and pork) (with a process tolerance of 20% in the modified environment, for a CO level of up to 0.48%). Precept estimated the amount of CO consumed using different scenarios based on basic assumptions. Cargill asserts that the assumptions put forth in GRN 143 apply to the current GRAS notice for CO use in a MAP system with fully cooked, sliced, pre-packed deli meats, and similar estimates of the amount of CO consumed are directly applicable.

- The following basic assumptions were made in GRN 143 about the MAP system tray size and product volume:
    - Assuming a fresh meat portion of 454 grams (g) and anticipated meat weight-to-gas volume ratio of approximately 0.8 to 1.0, a typical gas volume would be 363 mL or 0.363 L.
    - Assuming a maximum CO concentration of 0.48% in the MAP, CO is estimated to account for approximately 0.0017424 L or 1.74 mL CO per package.
    - CO is approximately 28 g per mole and 22.4 L/mole. The mass of CO per unit volume is thus 1.25 mg/mL (GRN 83):
        - (28 g/mol) ÷ (22.4 L/mol) = 1.25 g/L = 1.25 mg/mL
    - It has been reported that 30% of the CO in the MAP may be absorbed into packaged meat. Assuming that 30% is absorbed, the amount of CO absorbed into meat packaged in the Precept MAP is:

      0.3 x 1.74 mL/package x 1.25 mg/mL ÷ 0.454 kg/package = 1.44 mg CO/kg meat

- The following doses were estimated based on different consumption scenarios:

- Using a "worst-case" assumption, where 100% of the CO was taken up by the meat, with no reduction during cooking, a maximum theoretical CO content of the meat would be 4.79 mg CO/kg meat.

  1.74 mL/package x 1.25 mg/mL ÷ 0.454 kg meat/package = 4.79 mg CO/kg meat

- Thus, the worst-case ingestion scenario (100% of the CO in package was absorbed, 100% of the CO was consumed, and no reduction occurred during cooking) of an 8.8-ounce (250-g) serving would expose a consumer to **1.2 mg CO per meal**.

  4.79 mg CO/kg meat/package x 0.25 kg meat/meal = 1.2 mg CO/meal

- In another worst-case exposure scenario, wherein the consumer was exposed to 100% of CO in the package when the package was opened, the exposure would be **2.18 mg CO** (released to air to be breathed), an amount that is below well below the safety limit set by the EPA and OSHA.

  1.74 mL/package x 1.25 mg/mL = 2.18 mg CO in package released to air

These exposure scenarios described in GRN 143 are based upon larger serving sizes and packages than typically found in RTE meat and poultry. Therefore, these scenarios represent a "worst case exposure" scenario when considering sliced RTE meat and poultry.

§ 170.240 Part 4, Self-Limiting Levels of Use

The carbon monoxide ingredient is incorporated in a MAP system at a target level of 0.4% CO for use with cooked meat and is not intended to be used at levels above those specified in Part 3 above.

§ 170.245 Part 5, Experience Based on Common Use in Food

The statutory basis for our conclusion of the GRAS status of carbon monoxide for the proposed use in a MAP system for use with cooked meats in the notice is based on scientific procedures and not common use in food.

§ 170.250 Part 6, GRAS Narrative

History of Use and Regulatory Approvals

Published information and data have been submitted to and reviewed by FDA as part of other GRAS Notifications (GRNs) for several CO-related products. Previous GRNs have reviewed the safety of CO and concluded that the CO products were safe for their intended uses in human food. Table 2 below provides a summary list of such GRNs, all of which received "no objection" letters for their respective use(s) in food.

Table 2. GRAS Notifications relevant to a safety assessment of carbon monoxide

GRN No.	GRAS Substance	Intended Use	Year of Closure Reference	GRN Reference
251	Carbon monoxide	At a concentration of 0.4% as a component of a modified atmosphere system for fresh ground and muscle red meat.	FDA (2012a)	FDA (2008)
194	Carbon monoxide	As a dissolved gas at a concentration of 21.4 mL/L of brine/marinade solution that is injected into beef muscle parts that are vacuum-packed and prepared for case-ready marketing.	FDA (2012b)	FDA (2006)
167	Carbon monoxide	Use in MAP for red meat products.	FDA (2005b)	FDA (2005a)
143	Carbon monoxide	Use as a component of a MAP system for case-ready fresh beef and pork. [In this system, the MAP system has a target CO level of 0.4%, with a process tolerance of 20% in the modified environment, for a CO level up to 0.48%.]	FDA (2004b)	FDA (2004a)
83	Carbon monoxide	Use in the packaging of fresh cuts of muscle meat and ground meat as a component of a gas mixture in a MAP system. in fresh cuts of muscle meat or ground meat. [In the MAP system, CO is to be used at a target level of 0.4%.]	FDA (2002)	FDA (2001)
15	Tasteless smoke	Use in raw tuna, before it is frozen, to preserve its taste, aroma, texture, and color at levels sufficient to accomplish this purpose.	FDA (2000)	FDA (1999)

Safety

Safety Assessment of Carbon Monoxide

CO Safety — Introduction

CO is a colorless, odorless, and tasteless gas that is capable of causing acute and chronic toxicity in humans and animals at sufficient exposure concentrations. CO is ubiquitous,

and therefore, all humans are exposed to it at some concentration. It can come from natural, as well as anthropogenic sources. It can be produced as a pollutant from incomplete combustion of fossil fuel and biomass (e.g., internal combustion engines, wildfires). CO can be produced from photochemical oxidation of methane and other VOCs in the air. CO is emitted from vegetation into the air as a metabolic byproduct. Annual 24-hour average CO concentrations across all monitoring sites in the United States has been reported to be 1.2 ppm (1.4 mg/m^3) and about 0.2 ppm (0.3 mg/m^3) at rural sites. Indoor CO concentrations can vary based on the presence of combustion sources (e.g., fireplaces, wood-burning stoves, gas space heaters, smokers, presence of attached garages, etc.) Average CO concentrations in homes without gas stoves have been reported to range from 0.5 to 5 ppm. CO levels near properly adjusted gas stoves are approximately 5–15 ppm, and levels can be ≥30 ppm near those that are not properly adjusted. A study of homes with unvented natural gas fireplaces showed CO levels ranging from 1.5 to over 100 ppm during operation of the fireplace. Homes with attached garages had a net increase of <1 to 30 ppm CO after starting an automobile in the attached garage. Under standard smoking conditions, the emission of CO in mainstream smoke was 20.8 ± 1.9 mg CO per cigarette and 13.4 ± 1.6 mg CO/marijuana cigarette. CO emissions in side-stream smoke were 61.6 ± 2.9 mg and 50.6 ± 3.9 mg CO per cigarette for tobacco and marijuana cigarettes, respectively. CO levels in motor vehicles generally range between 9 and 25 ppm and can occasionally range to over 35 ppm (NAS, 2010; ATSDR, 2012). In the United States, CO has been used in vegetable processing since the 1970s to prolong the shelf life of lettuce during distribution. It has been recommended as a component of modified atmospheres to increase the shelf-life of various fruits and vegetables (e.g., cantaloupe, citrus, tomatoes, cauliflower) (Djenane and Roncales, 2018).

CO causes hypoxia by binding strongly to hemoglobin, forming carboxyhemoglobin (COHb), which reduces the oxygen-carrying capacity of the blood. The affinity of hemoglobin for CO is approximately 210 to 250 times higher than it is for oxygen. CO exposure is measured directly from blood as percentage of COHb or indirectly by the use of CO in expired breath. The main symptoms of CO intoxication are nonspecific, relating mainly to effects on the brain and heart (Smollin and Olson, 2008; Weaver et al., 2009). CO intoxication symptoms tend to correlate with an individual's peak blood COHb level. In general, symptoms and associated COHb concentrations (e.g., see Winter and Miller, 1976; Smollin and Olson, 2008; O'Malley and O'Malley, 2020) are shown in Table 3.

Table 3. Symptoms associated with varying concentrations of CO in air and COHb

CO in Air (%)	CO in Air (mg/m^3)	CO in Air (ppm)	COHb in Blood (%)	Physiological and Subjective Symptoms
0.007	80	70	10	No appreciable effect, except shortness of breath on vigorous exertion, possible tightness across the forehead, dilation of cutaneous blood vessel.
0.012	140	120	20	Shortness of breath on moderate exertion, occasional headache with throbbing in temples.
0.022	250	220	30	Decided headache, irritability, easily fatigued, judgement disturbed, possible dizziness, dimness of vision.
0.035–0.052	400–600	350–520	40-50	Headache, confusion, collapse, fainting on exertion.
0.080–0.122	900–1,400	800–1,220	60–70	Unconsciousness, intermittent convulsion, respiratory failure; death if exposure is of long duration.
0.195	2,200	1,950	80	Rapidly fatal.

Source (Winter and Miller, 1976; WHO, 1999).

Susceptible subpopulations are reported to be more sensitive to the effects of CO (NAS, 2010). Symptoms reported to be associated with COHb levels in susceptible populations are reported in Table 4 below and may occur at levels as low as 2%–3% COHb (e.g., FDA, 2001, 2004a). The Scientific Committee on Food states that COHb levels above 2% have been reported to have adverse effects, and levels below 2% do not have any measurable effects (SCF, 2001).

Table 4. Symptoms associated with COHb in susceptible subpopulations

COHb (%)	Symptoms
2	During physical exertion, reduced time to onset of angina and electrocardiogram signs of myocardial ischemia in subjects with coronary artery disease.
5–6	Increase in cardiac arrhythmias in subjects with coronary artery disease.
7	Headache, nausea in children.
13	Cognitive development deficits in children.
15	Myocardial infarction in subjects with coronary artery disease.
25	Syncope in children.
25	Stillbirths.

Source: NAS (2010).

Inhaled CO is quickly and extensively absorbed into blood (ATSDR, 2012). The ATSDR (2012) toxicological profile for CO stated that no information was available on the absorption or toxicity of oral exposure to gaseous CO. The elimination half-life of CO is about 4.5 hours with inhalation of room air, 1.5 hours using 100% oxygen, and 20 minutes using a hyperbaric chamber (oxygen under pressure). CO is exhaled via the lungs, and it is not metabolized or accumulated in the body (O'Malley and O'Malley, 2020; Yang et al., 2020).

The human body produces about 10 mL of CO per day. Approximately 1%–2% of human hemoglobin is bound with CO normally. Individuals in a busy urban or industrial setting may have COHb levels up to 5%. Smokers can have COHb levels ranging from 3% to ≤12% depending on the number of cigarettes smoked. Healthy heavy smokers can tolerate COHb concentrations up to 15%. COHb levels in newborns are ≥12% (Hampson et al., 2012; Katsnelson, 2019; Yang et al., 2020).

As mentioned above, CO is produced endogenously; similar to other endogenous gases that have both physiological and pathological significance (e.g., oxygen [O_2], nitric oxide [NO], and hydrogen sulfide [H_2S]). Over the past 20 years, researchers have been investigating the physiological role of CO. CO is formed in the body mainly from the oxidative breakdown of heme by microsomal heme oxygenases. Hemoproteins, including myoglobin, peroxidases, cytochromes, and catalase, can also contribute to the formation of endogenous CO (~20%–25%). Other sources of endogenous CO production include auto-oxidation of phenols, flavonoids, and halomethanes; photo-oxidation of organic compounds; lipid peroxidation of cell membrane lipids; and use of compounds that contain nicotinic acid, allyls (acetamids and barbiturates), diphenylhydantoin, progesterone contraceptives, and statins. In the body, CO can function as a neurotransmitter, with potential effects at low concentrations that include positive effects on inflammation, apoptosis, cell proliferation, oxidative stress, and up-regulation of mitochondrial biogenesis (Bauer and Pannen, 2009; EPA, 2010; Weaver et al., 2009; Goldberg and Holguin, 2013; Varma et al., 2015; Siracusa et al., 2021). As stated by Siracusa et al. (2021), "Every cell has a highly sophisticated system for regulating heme levels, which is particularly important with regard to turnover. Heme degradation generates CO, and while CO has long been viewed as a metabolic waste product, and at higher concentrations cellularly lethal, we now know that CO is an indispensable gasotransmitter that participates in fundamental physiological processes necessary for survival." CO levels in the body can fluctuate with various conditions and diseases (e.g., menstruation, pregnancy, anemia, and other hematologic disorders [EPA, 2010]).

There has been an interest in developing delivery vehicles for CO as a therapeutic, including CO-containing prodrugs (a compound that chemically reacts at the treatment site to release the bioactive molecule) in oral or intravenous forms or administered in a liquid formulation. Animal studies have suggested that a therapeutic dose of COHb is between 6% and 10%. It has been noted that the FDA limited CO exposures to 14% COHb in recent clinical trials (Hampson et al., 2012; Katsnelson, 2019; Yang et al., 2020). Siracusa et al. (2021) states that there are hundreds of reports in the literature of the benefits of low-dose

CO, which have led to many ongoing clinical trials (see their Table 1 for list). Siracusa et al. (2021) states that data from healthy human volunteers show no adverse events in individuals treated with CO sufficient to generate COHb levels of up to 14% (e.g., no headache, nausea, or dyskinesia).

CO Safety — Regulatory Precedent

Previous GRAS determinations on the safety of CO (FDA, 2001, 2004a, 2005a, 2006, 2008) relied on publicly available data that included background blood COHb concentrations, background CO levels in air, health-based US Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQSs) for CO and other environmental air regulatory levels, occupational values for CO established by the US Occupational Safety and Health Administration (OSHA) and other regulatory and health agencies, and other standards (e.g., FDA, 2004a). In addition, previous GRAS notifications cited experience with the use of CO in retail packaging and data from the published literature on the safe use of CO in case-ready meats (FDA, 2001, 2004; Cornforth and Hunt, 2008). A brief summary of relevant information from previous CO-related GRNs follows.

- GRN 15 (FDA, 1999; also cited in FDA 2004a,) proposed the use of tasteless smoke in raw tuna (prior to freezing) to preserve its taste, aroma, texture, and color. This GRN listed the main components of tasteless smoke as nitrogen and oxygen (45%–86%), carbon monoxide (7%–30%), carbon dioxide (7%–25%), and methane (<15%), along with trace levels of other compounds. In a comparison of CO levels in Albacore treated with raw smoke versus tasteless smoke, the concentrations ranged from 23 to 52 (no units provided) for the raw smoke and 19to 14 (no units provided) for the tasteless smoke. FDA (2000) published a "no questions" letter for GRN 15. GRN 15 also noted that conventional smoke—which contains CO as a one of its primary components—is GRAS:

  > *Conventional smoke is generally recognized as safe (GRAS). Although FDA has not specifically listed or affirmed it as GRAS, FDA is not required to do so under the Federal, Food, Drug and Cosmetic Act. Indeed, FDA specifically recognizes in its GRAS regulations that it is "impracticable to list all substances that are generally recognized as safe for their intended use." [21 CFR § 182.l(a)]. The GRAS status of conventional smoke is supported by the numerous food standards and other FDA regulations that specifically recognize the use of smoke as an ingredient in foods. For example, the standard of identity for canned tuna specifically allows the product to be smoked [21 CFR § 169.190(a)(3)(v)].*
  >
  > *In addition, there are numerous cheese standards of identity that specifically authorize for the smoking of cheese, including the standards for colby cheese, cold-pack cheese, cold-pack cheese food, pasteurized process cheese, pasteurize process cheese food, pasteurized process cheese spread, and provolone. The GRAS status of conventional wood*

smoke is further supported by its listing as an approved ingredient that may be added to meat and poultry products [9 CFR § 318.7(c)(4), 381.147(c)(4)].

- GRN 83 (FDA, 2001) proposed the use of a new system using 0.4% CO as a processing aid in a MAP system (the new system referred to as Active Tech 2001 or "AT2001") for fresh meat by Pactiv Corporation. GRN 83 estimated realistic and worst-case CO intakes per meal to be **0.084 mg** and **1.88 mg**, respectively. The CO intake assessment assumed that 100% of the CO in the MAP system was absorbed into the meat, with no reduction of CO during cooking. The assumptions and calculations for the CO intakes were as follows for a realistic CO intake per meal:

    - The AT2001 bag contained 1.5 L MAP with 0.4% CO = 0.006 L CO in the bag, or 6 mL CO.
    - At 28 g CO/mole and 22.4 L/mole, the mass of CO per unit volume is calculated as:

      (28 g/mol) ÷ (22.4 L/mol) = 1.25 g/L = 1.25 mg/mL
    - The AT2001 bag contains about 2 lbs, or ~1 kg, of ground meat.
    - About 30% of the CO is absorbed into the meat (per Watts et al., 1978), and to the amount of CO taken up by the meat is:

      0.3 x 6 mL/bag x 1.25 mg/mL ÷ 1.0 kg meat/bag = 2.25 mg CO/kg meat
    - Assuming that an individual consumes an 8.8-ounce steak (250 g = 0.25 kg) in a meal, an 85% reduction of CO during cooking, and 100% of the CO is absorbed, the maximum amount of CO in the meal is **0.084 mg/meal**.

      0.15 x 2.25 mg CO/kg meat ÷ 0.25 kg meat/meal = 0.084 mg CO/meal

    The assumptions and calculations for the CO intakes were as follows for a worst-case CO intake per meal:

    - Assume a 6-mg/mL bag; 1.25 mg/mL is the mass of CO per unit volume; assume 2 lbs (or ~1 kg) of ground beef/bag and consumption of 8.8 ounces of meat.
    - However, assume no reduction of CO during cooking; 100% of CO absorbed. The maximum theoretical CO exposure is **1.88 mg CO/meal**:

      7.5 mg CO/kg meat x 0.25 kg meat/meal = 1.88 mg CO/meal

    Based this assessment, GRN 83 stated that the consumption of meat treated with AT2001 "... is not expected to result in any measurable levels of carboxymyoglobin in the blood of those who consume treated meat." The FDA (2002) made a similar statement in its "no questions" letter; to wit: "...this MAP system complies with FDA's definition of a processing aid that appears in

labeling regulations (21 CFR 101.100(a)(3)). There is no lasting functional effect in the food and there is an insignificant amount of carbon monoxide present in the finished product under the proposed conditions of use" (FDA, 2001, 2004a).

- In 2002, Cryovac requested that a MAP system similar to that in GRN 83, and also using 0.4% CO, be deemed acceptable for use in packaging meat products from the US Department of Agriculture's (USDA's) Food Safety and Inspection Service (FSIS). On February 5, 2003, FSIS informed Cryovac that its system was acceptable for use (FDA, 2004a).
- GRN 143 (FDA, 2004a) was a GRAS notification from Precept Foods, LLC, for the use of a MAP system using a target concentration of 0.4% CO in case-ready fresh meat (beef and pork) (with a process tolerance of 20% in the modified environment, for a CO level of up to 0.48%). Precept estimated the amount of CO consumed using different scenarios based on basic assumptions:
    - The following basic assumptions were made about the MAP system tray size and product volume:
        - Assuming a fresh meat portion of 454 grams (g) and anticipated meat weight-to-gas volume ratio of approximately 0.8 to 1.0, a typical gas volume would be 363 mL or 0.363 L.
        - Assuming a maximum CO concentration of 0.48% in the MAP, CO is estimated to account for approximately 0.0017424 L, or 1.74 mL CO per package.
        - CO is approximately 28 g per mole and 22.4 L/mole. The mass of CO per unit volume is thus 1.25 mg/mL (GRN 83):

          (28 g/mol) ÷ (22.4 L/mol) = 1.25 g/L = 1.25 mg/mL
        - It has been reported that 30% of the CO in the MAP may be absorbed into packaged meat. Assuming that 30% is absorbed, the amount of CO absorbed into meat packaged in the Precept MAP is:

          0.3 x 1.74 mL/package x 1.25 mg/mL ÷ 0.454 kg/package = 1.44 mg CO/kg meat
    - The following doses were estimated based on different consumption scenarios:
        - Assuming the CO level is reduced by 85% during cooking (Sorheim et al., 1997), consumption of a cooked 8.8 ounces (250 g) meal of meat, with 100% of the CO in the meat being absorbed by the consumer, their intake would be **0.054 mg CO per meal.**

          0.15 x 1.44 mg CO/kg meat x 0.25 kg meat/meal = 0.054 mg CO/meal
        - Using a "worst-case" assumption, where 100% of the CO is taken up by the meat, with no reduction during cooking, a

maximum theoretical CO content of the meat would be 4.79 mg CO/kg meat.

1.74 mL/package x 1.25 mg/mL ÷ 0.454 kg meat/package = 4.79 mg CO/kg meat

- Thus, the worst-case ingestion scenario (100% of the CO in the package is absorbed, 100% of the CO is consumed, and no reduction occurs during cooking) of an 8.8-ounce (250-g) serving would expose a consumer to **1.2 mg CO per meal**.

4.79 mg CO/kg meat/package x 0.25 kg meat/meal = 1.2 mg CO/meal

- In another worst-case exposure scenario, where the consumer is exposed to 100% of CO in the package when the package is opened, the exposure would be **2.18 mg CO** (released to air to be breathed), an amount that is well below the safety limit set by the EPA and OSHA.

1.74 mL/package x 1.25 mg/mL = 2.18 mg CO in package released to air

- GRN 143 stated, "Accordingly, based on national, health-based standards for CO exposure, it may be persuasively concluded that the use of CO at 0.4% in a MAP system for fresh meats poses no health or safety concern and is not reasonably expected to result in any measurable levels of carboxymyoglobin in the blood of those who consume treated meat or who are nearby when one or more packages of case-ready meat are opened." Further, GRN 143 stated that their conclusion was consistent with that of Sorheim et al. (1997), who stated, "...it is highly improbable that CO exposure from meat packaged in an atmosphere containing up to 0.5% will represent a toxic threat to consumers through the formation of COHb."
- GRN 143 noted that, while there are differences between the "three systems" (Pactiv, Cryovac, Precept Foods MAP systems), "…these differences are not of toxicological significance..." (FDA, 2004a).
- In FDA's "no questions" letter for GRN 143, FDA stated, "Based on the information that you provide on behalf of Precept, as well as other information available to FDA, the agency has no questions at this time regarding Precept's conclusion that CO is GRAS under the intended conditions of use" (FDA, 2004b).
- GRN 167 (FDA, 2005a) from Tyson Foods, Inc., proposed the use of 0.4% CO in MAP packaging for red meat products. Tyson's product used a reduced-headspace system and a higher CO concentration per unit volume in their product. A "no questions" letter was issued by the FDA (2005b). It was estimated that the CO exposure would be **0.054 mg** CO per meal of cooked meat, assuming that the meat absorbed 30% of the CO, and 100% of the CO was absorbed by the consumer. When 8.8 ounces (250 g) of meat is consumed, the dietary intake would be **0.36 mg of CO** per meal. (Note that the 85% reduction in CO from cooking decreases the exposure from 0.36 mg to

0.054 mg CO per meal.) If 100% of the CO was absorbed and 100% was consumed, an 8.8-ounce serving would equal a dose of **1.2 mg CO** for the consumer (FDA, 2005a,b).

- GRN 194 was submitted by Freezing Machines, Inc., for the use of CO in brines and marinades to be injected into beef muscle products. The GRN stated that the amount of CO in the processed meat using this application would be equal to or less than the levels that would be present from the applications defined in previous GRNs (e.g., 1.88 mg/250 grams of red meat in the pre-cooked product). GRN 194 further states, "The use of CO proposed herein will not result in any increased dietary exposure to CO. The dietary exposure will not increase because the potential concentration of CO in red meat processed using the method described in this Notice will be less than or equal to the levels that are expected to result from the applications detailed in the previous Notices... Since neither the concentration of CO in the processed food nor new applications for CO will result from the use described herein, there will be no increase in total dietary exposure. Therefore, the data used to support the three effective GRAS Notices also demonstrate the safety of CO in this application." The use of the process will limit the quantity of CO to **1.3 mg**/250-g serving of meat. Assuming that 85% of the CO would volatilize during cooking, the remaining CO after cooking would be **0.195 mg** (1.3 mg x 0.15). (FDA, 2006). A "no questions" letter was issued by the FDA in 2012 (FDA, 2012b).
- GRN 251 (FDA, 2008) was submitted to the FDA by Vincent Mercogliano for the use of CO (0.4%) as a component of a MAP system for ground beef and red muscle meat ("M-V process"[1]). This GRN stated that it relied on "FDA's response letters to related GRAS notices, on published studies, on the generally accepted method of vacuum packaging for extending the shelf life of meat, and on generally accepted scientific data as the basis for its conclusions on the safety of a modified atmosphere packaging system for fresh meat that utilizes 0.4% CO in the inert gas helium, followed by vacuum packaging." FDA (2012b) issued a "no questions" letter.
- The Scientific Committee on Food of the European Commission provided an opinion in 2001 that meat packaged in MAP containing a high level of CO_2 and 0.3% to 0.5% of CO would contribute a negligible amount to the overall exposure to CO and COHb level in humans (SCF, 2001).
    - SCF stated that an assumed consumption of 250 g fresh meat/24 hours could release 0.18 mg CO (equal to 0.018% COHb) on digestion in the gut. Assuming 100% transfer of CO from the gut to the blood and complete transformation of COHb, only a negligible amount of COHb

[1] M-V process described in GRN (2008): "Because the M-V process allows only shallow penetration of the treated meat surfaces by the treatment gas, any unreacted carbon monoxide will be readily removed in the second vacuum treatment. Moreover, carboxymyoglobin forms only on the very surface of the meat and is readily destroyed immediately upon grilling or roasting the meat. This is in contrast to MAP systems that allow uncontrolled penetration by CO, since overcooking may then be required to decompose all carboxymyoglobin (as evidenced by color change)."

would be added to the 0.5% COHb that results from endogenous CO production and the 0.7%–1.0% formed from inhalation of urban air (non-smokers). Exposure through inhalation of headspace gas on opening a package of meat with a MAP containing 0.3%–0.5% CO would contribute insignificantly to the COHb compared to other inhalation CO sources.

- The SCF (2001) noted that MAP of fresh meat using high-CO_2/low-CO mixtures had been used in Norway since the mid-1980s, with 50%–60% of the retail meat and up to 85% of the ground beef being packaged under those conditions.

- New Zealand and Australia regulate low CO levels in centralized packaging systems, and it is also considered a processing aid (Van Rooyen et al., 2017).
- Canada allows the use of 0.4% CO as a secondary packaging gas (USDA-FSIS, 2016, as cited in Djenane and Roncales, 2018).

CO Safety — Basis for GRAS Determination

Table 5 lists various occupational and non-occupational regulatory standards (inhalation) for CO.

Table 5. Regulatory standards for carbon monoxide

Regulatory/Agency Standard	Value	Reference
Non-occupational		
ATSDR Oral MRL	NA	ATSDR (2021)
ATSDR Inhalation MRL	NA	ATSDR (2021)
JECFA/WHO ADI	NA	JECFA/WHO (2021)
EPA NAAQS* 8-hour 1-hour	 9 ppm (10 mg/m^3) 35 ppm (40 mg/m^3)	EPA (2021)
Occupational		
OSHA PEL (8-hour)	50 ppm (57 mg/m^3)	NIOSH (2019)
ACGIH TLV-TWA (8-hour)	25 ppm (29 mg/m^3)	ACGIH (2020)

NA: none available. TWA: time-weighted average.

*Not to be exceeded more than once per year.

Non-Occupational Standards

As can be seen in Table 5 above, no Joint FAO/WHO Expert Committee on Food Additives (WHO/JECFA) acceptable daily intake (ADI) or Agency for Toxic Substances and Disease Registry (ATSDR) oral or inhalation minimal risk level (MRL) values have been identified for CO (FDA, 2001). However, GRN 83 (FDA, 2001) noted that exposure to CO at levels

higher than 0.4% have been permitted by the FDA in tasteless smoke (see above) and foods and beverages:

- The specification for "Combustion product gas" in 21 CFR § 173.350 permits CO use up to 4.5% (by volume) in the processing, storage, and packaging of beverages and foods (except fresh meats) to remove and displace oxygen (FDA, 2004a, 2021).

EPA has set CO primary 8-hour and 1-hour air National Ambient Air Quality Standards (NAAQS) of 9 ppm (10.3 mg/m^3) and 35 ppm (40.1 mg/m^3), respectively, which are not to be exceeded more than once per year. Primary health standards are protective of human health, including "sensitive" populations (e.g., asthmatics, children, and elderly) (EPA, 2021).

Consumption of meat treated with CO using this MAP system is not expected to result in a toxicologically meaningful increase in COHb in the blood of consumers who might ingest CO-treated meat. A comparison of the estimated daily intake of CO from CO-treated meat using the estimated intake values from GRN 143 (e.g., **0.054–2.18 mg CO per event**) can be compared to the allowable regulatory values for CO. For example:

- 8-hour EPA NAAQS: The EPA 8-hour NAAQS for CO is 9 ppm, or 10 mg/m^3. Assuming that the average individual breathes 15 m^3 of air/day, or 5 m^3/8 hours, the allowable amount of CO in 8 hours would be 52 mg. Using the various meat intake values calculated in GRN 143, the CO amount from meat is shown as a percentage of the NAAQS value below (FDA, 2004):
    - Use in the MAP system (with an 85% reduction of CO from cooking) would represent only **0.1%** of the 8-hour CO NAAQS [0.054 mg CO/52 mg CO x 100]
    - Worst-case scenario in the MAP system (with no reduction of CO from cooking) would equal **2.3%** of the 8-hour CO NAAQS [1.2 mg CO/52 mg CO x 100]
    - Worst-case where consumer is exposed to 100% of CO in package (2.18 mg CO) would be equal to **4.2%** of the 8-hr CO NAAQS [2.18 mg CO/52 mg CO x 100]
        - Stated a different way, assuming a small room of 30 m^3 in volume, opening one bag would contribute 0.073 mg^3 to the CO level in air (0.7%) of the NAAQS of 10 mg/m^3. Using this rate, approximately 142 bags would need to be opened for the air in the room to reach the EPA standard (assuming that no air exchanges are occurring) (FDA, 2004a).
- OHSA 8-hour PEL: Similarly, a comparison can be made to the federal occupational inhalation standard for an 8-hour exposure to CO of 50 ppm (57 mg/m^3). This concentration would be expected to result in an exposure of

285 mg CO (assuming that workers inhale 5 m^3 air in an 8-hour workday) (57 mg/m^3 CO x 5 m^3) (FDA, 2004):

- Using the MAP system where the CO is reduced 85% by cooking would be only **0.019%** of the OSHA PEL [0.054 mg CO ÷ 285 mg CO x 100]
- Use of the MAP where no CO reduction occurs during cooking would equal only **0.4%** of OSHA PEL [1.2 mg CO ÷ 285 mg CO x 100]
- Worst-case scenario, where a consumer is exposed to 100% of CO in package, would equate to just **0.8%** of the OSHA PEL [2.18 mg CO ÷ 285 mg CO x 100]

- ACGIH TLV-TWA: Another comparison can be made to the amount inhaled during an 8-hour period at the ACGIH TLV-TWA for CO of 25 ppm (29 mg/m^3) (GRN 83). Assuming that an individual breathes 5 m^3 air in 8 hours, the concentration would result in an exposure of 145 mg CO in 8 hours (29 mg CO/m^3 x 5 m^3).
  - Using the MAP system in which the CO is reduced 85% by cooking would be only **0.037%** of the ACGIH TLV [0.054 mg CO ÷ 145 mg CO x 100]
  - Use of the MAP system in which no CO reduction occurs during cooking would equal **0.8%** of the ACGIH TLV [1.2 mg CO ÷ 145 mg CO x 100]
  - Worst-case where consumer is exposed to 100% of CO in package would be just **1.5%** of the ACGIH TLV [2.18 mg CO ÷ 145 mg CO x 100].

These calculations demonstrate that the estimated daily intake of CO from consuming packaged meat is only a small fraction of the exposures currently allowed by several regulatory bodies.

In addition, Sorheim et al. (1997) compared CO exposure from the air to the estimated exposure from CO-treated meat. As can be seen in Table 6 below (from Sorheim et al., 1997), the amount of CO ingested from meat is far less than that inhaled from either 24 mg/m^3 (21 ppm) for 1 hour or 9.2 mg/m^3 (8 ppm) for 8 hours (the maximum CO concentrations and time in air that are reported to not be exceeded in order for COHb levels in blood not to exceed 1.5%). The amount of CO in meat are far lower than the amounts from exposure in air during moderate physical activity. Sorheim et al. (1997) concluded (FDA, 2001):

> *In order to prevent a maximum COHb level in the blood of 1.5% being exceeded, the CO concentration in air for a 1-h period of moderate physical activity should not exceed 24mg/m3, or 9.2 mg/m3 in 8 h (according to Table 4). In contrast, the consumption of meat that had been treated for 3 d in an atmosphere containing 1% CO yielded ~0.1 mg of CO per kg of meat on storage and cooking.*

Table 6. Theoretical uptake of CO in blood

Exposure Method	CO intake in 1 hour	CO intake in 8 hours
Lungs (15 m^3/day)	24 mg x 0.625 = 15.1 mg	9.2 mg x 5 = 46.0 mg
Meat (250 g; CO treated)	0.025 mg	0.025 mg

Source: Sorheim et al. (1997)

The lack of any expected significant increase in COHb or health risks associated with the MAP system containing 0.4% CO is also consistent with the comments made in a recent review of this subject by Djenane and Roncales (2018):

> *The toxicological aspects of CO used in MAP of meat were reviewed by Sorheim et al., and they concluded that, with up to about 0.5% of CO, no human toxicity was likely. Sorheim et al. and Cornfort and Hunt found that consumption of CO-treated meat is not associated with any health risks, and meat from CO-MAP results only in negligible amounts of CO and COHb in humans. The Norwegian Food Control Authority (NFCA) has not registered outbreaks or a higher frequency of sporadic cases of food-borne diseases linked to such products since 1985. The increased red color stability of meats exposed to CO was recognized more than 100 years ago [180]. However, the application of CO in meat packaging was not then considered feasible because of possible environmental hazards for workers. For safety reasons, gas detectors are necessary in environments in which CO is applied in any form. Nowadays, exposure to CO in an industrial setting (meat industry) is associated with minimal risks, both due to good practice at the working facilities and equipment design. Human environmental exposure to CO varies greatly. In the same order of ideas, Sorheim et al. indicated that the max level of COHb is recommended to not exceed 1.5%. A COHb level of less than 5% in human blood is not associated with any harm to healthy individuals, and the half-life of COHb in individuals is approximately 4.5 h. The same authors indicated that during various decades of low CO-MAP in the Norwegian meat industry, its use was not associated with any risks to workers.*
>
> and,
>
> *Recently, an attempt to calculate the COMb in a package atmosphere and very interesting findings have emerged concerning CO and consumer safety. Based on the fact that the typical meat packages have a headspace of 1.5 L and the ambient air quality standard for CO inhalation is 9 ppm/8 h, fresh packaged meat stored in low CO-MAP with a 1.5-L headspace could contain 0.4% CO. Opening one CO-MAP container in an average space (150 m3) results in an ambient air CO concentration of 0.042 ppm.*

Assuming that no COMb has developed, opening one CO-MAP container in 0.8% CO with a 0.4-L headspace results in 0.022 ppm CO in ambient air. After 7 days of display, 9100 of the packages with 0.8% CO in a 0.4-L headspace would have to be opened in one room (150 m3) to meet the EPA standard of 9 ppm CO. Thus, reducing headspace from 1.5–0.4 L and increasing CO from 0.4–0.8% do not pose a consumer safety risk [107]. For low CO-MAP (0.4% CO) with a 1.5-L headspace, opening of 216 packages for the same area would be required to exceed the EPA standard for a typical person inhaling 5 m3 air/8 h. On the other hand, an assumed consumption of 250 g fresh meat/day could therefore release 0.18 mg CO (~0.018% COHb). If there were a 100% transfer of CO from the gut to the blood, only a negligible amount of COHb would be added to the 0.5% COHb, resulting from endogenous CO production, and ~1.0% COHb formed from inhalation of the contaminated atmosphere by a non-smoker. Realistically, one would consume even less CO per meal because it is known that only 15% of bound CO remains with the meat after cooking. Exposure through inhalation of headspace gas on opening a package of meat with a MAP containing 0.3–0.5% CO would equally contribute insignificantly to the COHb in the blood when compared to the other sources of inhalation of CO.

In summary, the safe use of CO in a MAP system with cooked meats is supported by a long history of regulatory approvals for use of similar products and the available safety-related data specific to carbon monoxide.

Basis for the GRAS Determination

Introduction

The regulatory framework for determining whether a substance can be considered GRAS in accordance with Section 201(s) (21 U.S.C. § 321(s)) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 301 et. Seq.) ("the Act"), is set forth at 21 CFR 170.30, which states:

> *General recognition of safety may be based only on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.*
>
> *General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data and information.*

These criteria are applied in the analysis below to determine whether the use of carbon monoxide in a MAP system with cooked meats is GRAS based on scientific procedures. All data relied upon in this GRAS determination are publicly available and generally known, and therefore meet the "general recognition" standard under the FFDCA.

General Recognition of the Safety of Carbon Monoxide

The intended use of carbon monoxide has been determined to be safe through scientific procedures, as set forth in 21 CFR § 170.3(b), thus satisfying the so-called "technical" element of the GRAS determination, and this determination is based on the following:

- Carbon monoxide is intended for use as a component of a modified atmosphere packaging (MAP) system for fully cooked, sliced, pre-packed, ready-to-eat (RTE) deli meats. As in GRAS Notification 143, carbon monoxide will be used at a target concentration of 0.4% or less (with a process tolerance of 20% in the modified environment, for a CO concentration of up to 0.48%). CO will be used in a mixture of nitrogen (0–100%) and carbon dioxide (0%–100%).
- The proposed use of the MAP system containing CO with fully cooked deli meats is identical to that described in GRN 143 (part III) for fresh meat products. The use of CO is meant only to stabilize the color of the meat and does not affect microbial growth. The proposed system is not intended to extend the shelf life of cooked deli meat products in excess of the shelf lives already established for similar MAP systems.

- Carbon monoxide is a colorless, odorless gas that has a density slightly less than air. CO is ubiquitous, and therefore, all humans are exposed to it at some concentration. It can come from natural as well as anthropogenic sources.
- The CO used in the MAP system is food-grade quality and calls for a minimum CO content of 98%, the same as the specifications put forth in GRN 143. Any impurities present would consist of components found in the atmosphere, such as N_2, O_2, CO_2, argon, H_2O, H_2, and/or CH_4.
- A representative worst-case consumption estimate of CO is as follows: worst-case ingestion scenario (100% of the CO in package is absorbed by the cooked meats, 100% of the CO is consumed, and no reduction occurs during cooking or other processes) of an 8.8-ounce (250-g) serving would expose a consumer to **1.2 mg CO per meal**.
- In a further worst-case exposure scenario, wherein the consumer is exposed to 100% of CO in the package when it is opened, the exposure would be **2.18 mg CO** (released to air to be breathed), an amount that is below well below the safety limit set by the EPA and OSHA.
- The exposure scenarios described in GRN 143 are based upon larger serving sizes and packages than typically found in RTE meat and poultry. Therefore, these scenarios represent a "worst case exposure" scenario when considering sliced RTE meat and poultry.
- The Scientific Committee on Food of the European Commission provided an opinion in 2001 that meat packaged in MAP containing a high level of CO_2 and 0.3% to 0.5% of CO would contribute a negligible amount to the overall exposure to CO and COHb level in humans.
- Consumption of meat treated with CO using this MAP system is not expected to result in a toxicologically meaningful increase in COHb in the blood of consumers who might ingest CO-treated meat. This is evident from a comparison of the estimated daily intake of CO from CO-treated meat using the estimated intake values from GRN 143 (e.g., **0.054–2.18 mg CO per event**) and comparison to the allowable regulatory values for CO.
- The body of publicly available scientific literature on the consumption and safety of carbon monoxide as proposed for use in a MAP system with cooked deli meats is sufficient to support the safety and GRAS determination of the proposed use of carbon monoxide.

This safety evaluation was based on generally available and widely accepted data and information; therefore, it also satisfies the so-called "common knowledge" element of a GRAS determination.

Determination of the safety and GRAS status of carbon monoxide that is the subject of this GRAS self-determination has been made by Cargill and Dr. Mindy Brashears. Dr. Brashears' expert opinion is attached as Exhibit 1. Cargill has commissioned ToxStrategies to critically review and evaluate the publicly available information summarized in this

document, and on the basis of that assessment, has concluded that the proposed use of carbon monoxide, produced in a manner consistent with cGMP and meeting the specifications described herein, is safe under the intended conditions of use. Cargill also concludes that the proposed use of carbon monoxide is GRAS based on scientific procedures, and that other experts qualified to assess the safety of foods and food additives would concur with these conclusions. Therefore, it is excluded from the definition of a food additive and may be marketed and sold for its intended purpose in the US without the promulgation of a food additive regulation under Title 21 of the CFR.

Cargill is not aware of any information that would be inconsistent with a finding that the proposed use of carbon monoxide is GRAS. Recent reviews of the scientific literature revealed no potential adverse health concerns.

§ 170.255 Part 7, Supporting Data and Information

The following references are all generally available, unless otherwise noted. Appendix A is not generally available but is attached for reference.

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APPENDIX A

Shelf-Life Study Report

Shelf Life Summary- Carbon Monoxide Use in Cooked Beef GD210208

Overview

Project Title	*Grab n Go Sliced Roast Beef in CO*
Project ID	*GD210208*
Sampling Method	*20g*
Objective	*Compare shelf-life of current product versus new test product with CO*
Production Date	*1/25/21*
Plant/Establishment #	*86X CIC*
Customer/Scientist	*Retail/Garret Dietz*
Storage Temperature	*45F dark storage*
Did the product(s) achieve desired shelf-life?	*See 'Conclusion and Recommendations' section*

Protocol

Beef inside muscles were injected with a solution, tumbled, and placed into a cook-in-bag before cooking to an internal temperature of 140°F. Cooked beef inside muscles were then sliced at 2.0 mm and placed into either a modified atmosphere package with 70% Nitrogen and 30% Carbon Dioxide (Control) or a modified atmosphere package with 69.6 % Nitrogen, 30% Carbon Dioxide, and 0.4% Carbon Monoxide (CO Test). Product was then placed into a cooler at 45°F. Product was evaluated every 14 days for 70 days for Aerobic Plate Count, Lactic Acid Bacteria/Anaerobic Plate Count, Organoleptic odor and color.

Key Findings

- *Aerobic Plate Count (figure 1)*
  - *Control mean growth peaked at a level in excess of 9.00 logs cfu/g by 56 days of age*
  - *CO Test mean growth achieved an apparent stationary level ≥8.00 logs by 42 days of age*

- *Lactic Acid Bacteria/Anaerobic Plate Count (fig 1)*
  - *Control mean growth peaked at a level in excess of 9.00 logs by 56 days of age*
  - *CO Test mean growth achieved an apparent stationary level ≥8.00 logs by 42 days of age*

- *Organoleptics (fig 2)*
  - *Control mean Odor and Color scores remained high to marginally acceptable for the duration of the study: 70 days of age*
    - *Variations in acceptability was the result of the presence of brief sulfuric and sour off odors*
  - *CO Test mean Odor and Color scores remained highly acceptable for the duration of the study*
  - *CO Test product maintained a bolder, and brighter red color versus Control product for the duration of the study*

Conclusion and Recommendations

- ***Control product remained acceptable through 70 days of age.***

- ***CO Test product remained acceptable through 70 days of age.***

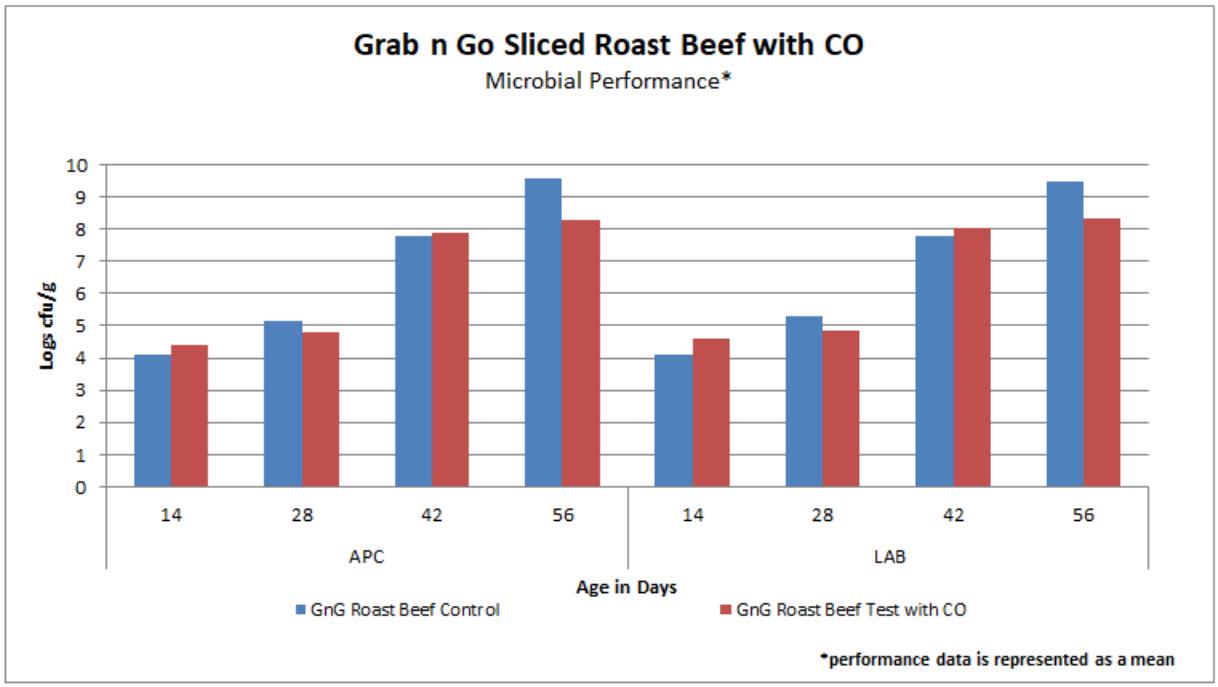
- ***Control product remained a consistent gray well done cooked beef color throughout the entire shelf life, while the CO Test product remained consistent red medium-rare cooked beef color throughout the entire shelf life.***

- ***The indicators of spoilage (odor, APC growth, LAB growth) were similar for both treatments, regardless of the color of the product.***

Shelf Life Summary- Carbon Monoxide Use in Cooked Beef GD210208

Figures and Tables

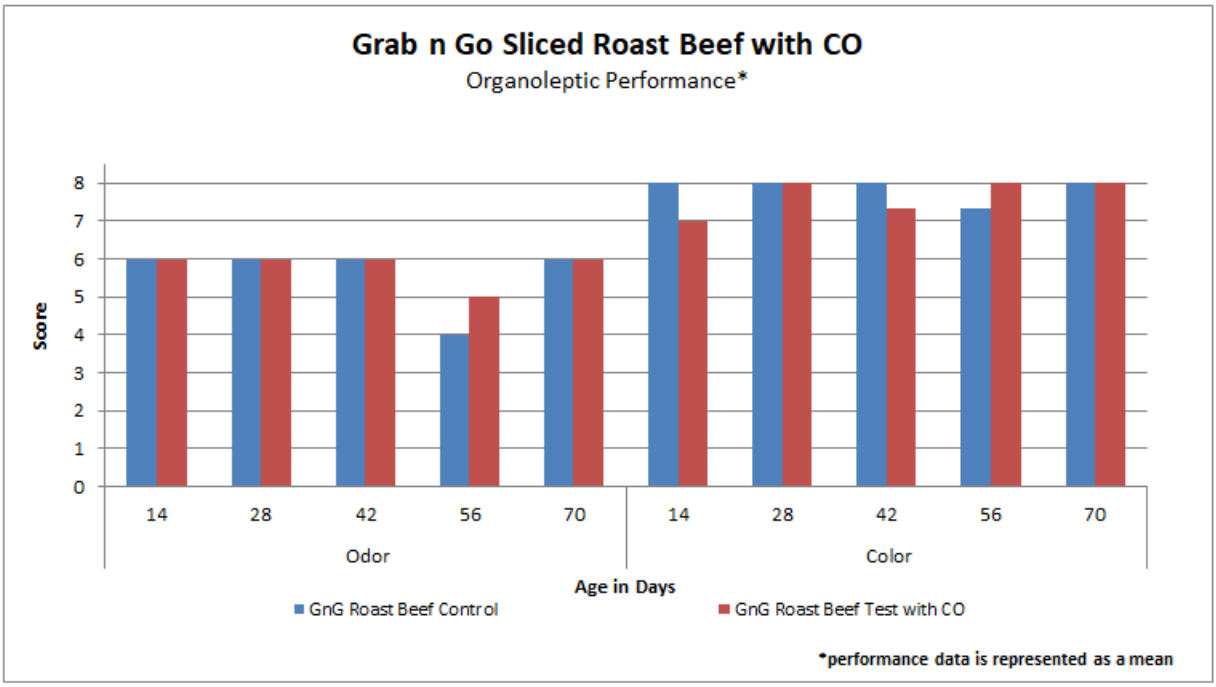
Figure 1



*Microbiological performance was not measured after Day 56 due to counts being above 8 logs cfu/g

Shelf Life Summary- Carbon Monoxide Use in Cooked Beef GD210208

Figure 2



1. Organoleptic Evaluation Classifications of Products' Shelf Life

a. **Color of the meat**

8	Extremely desirable or acceptable
7	Very desirable or acceptable
6	Moderately desirable or acceptable
5	Slightly desirable or acceptable (still would eat)
4	Slightly undesirable or unacceptable (would not eat)
3	Moderately undesirable or unacceptable
2	Very undesirable or unacceptable
1	Extremely undesirable or unacceptable

b. **Product odor upon the opening of the package**

6	No odor (unless product contains spices with acceptable odor)
5	Slight odor, dissipates quickly
4	Slight odor remains (would still eat)
3	Slight odor remains (would not eat)
2	Moderate off odor
1	Strong offensive off odor

Shelf Life Summary- Carbon Monoxide Use in Cooked Beef GD210208

	Name	*Title*	*Date*
Submitted by:	*Kevin Kroeger*	*CIC lab*	*4/13/21*
Revised by:			
Reviewed by:			
Approved by:			
Revision History:			

EXHIBIT I

Expert Opinion of Mindy Brashears, Ph.D.

TEXAS TECH UNIVERSITY
College of Agricultural Sciences & Natural Resources
Department of Animal and Food Sciences

June 6, 2021

To: Scott Eilert
Cargill

From: Mindy Brashears, PhD [redacted]
Roth and Letch Family Endowed Chair in Food Safety
Associate Vice President for Research

Subject: Use of Carbon Monoxide Packaging for Deli Meats
Expert Opinion

Having studied food safety microbiology for my entire professional career that spans 23 years, specializing in meat safety, I am prepared to give an expert opinion on the suitability of the use of carbon monoxide packaging for use in deli meats. I studied the use of carbon monoxide packaging and its impact on meats from a microbiological perspective and have published the results of those findings (available upon request). When I refer to Carbon Monoxide Packaging or CO packaging, I am specifically referring to a Modified Packaging System (MAP) that contains a low-oxygen environment with up to 0.4% CO with the remaining atmosphere containing CO_2 and N. the CO system is an important technology for use in the meat industry providing a measure of safety and protecting the shelf-life of the product.

The use of CO packaging was approved for use under GRAS 143 for raw meat products. At Texas Tech we published studies related to the use of the CO packaging containing 0.4% CO alongside the use of "Traditional" MAP which would contain O_2 and CO_2. In our studies we concluded the CO packaging had a stabilizing effect on the color of the beef patties. However, of utmost importance, consumers were able to detect spoilage in both types of MAP packages over time as expected. In both types of MAP packaging, there was significantly less *E. coli* O157:H7 and *Salmonella* compared to an overwrap package over the course of the shelf life. Neither type of MAP package resulted in a product that was spoiled microbiologically but not able to be determined to be spoiled by the consumer. This study was conducted under typical storage conditions as well as temperature abuse conditions to mimic the abuse a product might receive when handled by a consumer. Similar results were obtained with both the CO packaging and the High Oxygen MAP systems being superior to the overwrap system. Consumers could detect spoilage when the product was stored at a constant refrigerated temperature and during temperature abuse conditions as well.

Given my past experience as a scientist studying these MAP packing systems, it is my expert opinion that the use of GRAS 143 should be considered to be applied to the cooked meats under this same GRAS notice. Currently, the CO systems can be used for deli meats that are case-ready and packed in an establishment. Case ready products packaged in the facility have a reduce risk of microbial contamination due to less handing. When sliced in an inspected establishment, HACCP, Sanitation Standard Operating Procedures, and a *Listeria* control plan must be in place. The environment alone and the reduction in risk to the consumer warrants careful consideration. Given the reduction in the risk of contamination and the potential for preventing future illnesses, the use of this technology system should be approved as quickly as possible.

To address microbial concerns that might arise with this packaging, I will first mention that the risk is much lower due to the nature of the product. Any vegetative pathogen such as *Salmonella* or Shiga-Toxin Producing *E. coli* (STEC) would be killed by the cooking/lethality process during production. Spore-forming pathogens must be addressed during stabilization (chilling) and thus they are not a concern. FSIS requires validated lethality and stabilization processes to be in place under Appendix A and B. Additionally, there is a regulatory requirement for control of *L. monocytogenes*. These plans, in general, allow for various combinations of control from sanitation programs to microbial testing to the use of anti-microbials in the product. In the case of Cargill, they use anti-microbial ingredients in their products to prevent the outgrowth of *L. monocytogenes*. The growth/survival of spoilage or background flora in the deli meats offers no control of the pathogens in the product unless they are applied as a biological control system. I am very confident to say that CO should not have any impact on microbial outgrowth as compared to MAP packages without CO. This is based on my experience as a microbiologist, specifically studying MAP packing systems in meats.

Deli meats also have a shelf-life that is indicated on the packaging by a printed date. While the consumer might rely more heavily on the outgrowth of the natural flora in raw products to determine if the product is spoiled, the shelf-life limits the time the product can be used as opposed to visual observations for spoilage.

Given the need to reduce the risk to the consumer and the fact that there is little impact on the natural flora in terms of pathogen control or shelf-life/spoilage indication to the consumer, it is reasonable for this technology to be considered GRAS under a GRAS submission.

From: Don Schmitt
To: Kampmeyer, Christopher
Cc: Alex Eapen
Subject: [EXTERNAL] Re: Request regarding your submission for carbon monoxide
Date: Tuesday, August 17, 2021 5:30:25 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image007.png
Page 7.pdf

Dear Chris,

On behalf of Cargill, please find attached a revised page 7 of their carbon monoxide GRAS notice, including my signature and a revised FSIS statement per Cargill.

Best regards,

Don

Donald F. Schmitt, M.P.H.
Senior Managing Scientist

ToxStrategies, Inc.
739 Thornapple Drive
Naperville, IL 60540
phone: 630.352.0303
email: dschmitt@toxstrategies.com

From: "Kampmeyer, Christopher" <Christopher.Kampmeyer@fda.hhs.gov>
Date: Monday, August 16, 2021 at 3:31 PM
To: "Donald Schmitt, MPH" <dschmitt@toxstrategies.com>
Subject: Request regarding your submission for carbon monoxide

Dear Mr. Schmitt:

I am writing regarding your submission dated June 10, 2021, regarding uses of “carbon monoxide” in food to the GRAS Notification Program. During our prefiling evaluation, we noted that your GRAS notice is missing your signature in part one of the notice. Additionally, on the same page, please clarify your “FSIS statement” to explicitly state that you authorize us to send any trade secrets to the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture; or a statement asking us to exclude any trade secrets from the copy of the GRAS notice that we will send to FSIS, per §170.225)(c)(11). Could you please provide me a revised and signed copy of this one page? Alternatively, please request that we cease to evaluate this submission and resubmit the notice (with signature and clarification) in its entirety.

Thank you,
Chris

Chris Kampmeyer, M.S.
Regulatory Review Scientist

Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
christopher.kampmeyer@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

(7) Availability of Information

The data and information that serve as the basis for this GRAS determination, as well any information that has become available since the GRAS determination, will be sent to the FDA on request and are also available for the FDA's review and/or copying during customary business hours, from ToxStrategies, Inc., Naperville, IL.

(8) Data and Information Confidentiality Statement

None of the data and information in the GRAS notice is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

(9) GRAS Notice Certification

To the best of our knowledge, the GRAS notice is a complete, representative, and balanced submission. Cargill is not aware of any information that would be inconsistent with a finding that the proposed use of CO in food, that meets appropriate specifications and is used according to current Good Manufacturing Practice (cGMP), is GRAS. In addition, recent reviews of the scientific literature indicated no concerns for potential adverse health effects.

(10) Name/Position of Notifier

[redacted]

August 17, 2021
Date

Donald F. Schmitt, M.P.H.
Senior Managing Scientist
ToxStrategies, Inc.
Agent for Cargill

(11) FSIS Statement

As described above, CO will be used in fully cooked, sliced, pre-packed, RTE deli meats (including but not limited to beef, pork, and poultry) in a MAP system in a fashion similar to that described in GRAS Notification (GRN) 143, which proposed the same use in fresh beef and pork, as opposed to cooked meats, as discussed in this GRAS notice. Cargill authorizes FDA to send any trade secrets to the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture, maintaining the designation of that information as trade secret and not subject to disclosure under FOIA.

Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022
(See last page for OMB Statement)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE (Subpart E of Part 170)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: 2021-02-16

4 For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd)*: _____

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Alex Eapen	Director

Organization *(if applicable)*: Cargill, Inc.

Mailing Address *(number and street)*: 15407 McGinty Road West

City	State or Province	Zip Code/Postal Code	Country
Wayzata	Minnesota	55391	United States of America

Telephone Number	Fax Number	E-Mail Address
952-742-4497		alex_eapen@cargill.com

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position or Title
Donald Schmitt	Senior Managing Scientist

Organization *(if applicable)*: ToxStrategies

Mailing Address *(number and street)*: 739 Thornapple Drive

City	State or Province	Zip Code/Postal Code	Country
Naperville	Illinois	60540	United States of America

Telephone Number	Fax Number	E-Mail Address
630-352-0303		dschmitt@toxstrategies.com

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

Carbon monoxide

2. Submission Format: *(Check appropriate box(es))*

☒ Electronic Submission Gateway

☐ Electronic files on physical media

☐ Paper

If applicable give number and type of physical media

_____

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

4. Does this submission incorporate any information in CFSAN's files? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for conclusions of GRAS status *(Check one)*

☒ Scientific procedures *(21 CFR 170.30(a) and (b))* ☐ Experience based on common use in food *(21 CFR 170.30(a) and (c))*

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

SECTION D – INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

Carbon monoxide is intended for use as a component of a modified atmosphere packaging system for fully cooked, sliced, pre-packed, ready-to-eat (RTE) deli meats and poultry. As in GRAS Notification 143, carbon monoxide will be used at a target concentration of 0.4% or less (with a process tolerance of 20% in the modified environment, for a CO concentration of up to 0.48%). CO will be used in a mixture of nitrogen (0–100%) and carbon dioxide (0%–100%).

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☒ Yes ☐ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☒ Yes ☐ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete – PART 1 is addressed in other sections of this form)

☒ PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).

☒ PART 3 of a GRAS notice: Dietary exposure (170.235).

☒ PART 4 of a GRAS notice: Self-limiting levels of use (170.240).

☒ PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).

☒ PART 6 of a GRAS notice: Narrative (170.250).

☒ PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that Cargill, Inc.
(name of notifier)

has concluded that the intended use*(s)* of Carbon monoxide
(name of notified substance)

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. Cargill, Inc. agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so; agrees to send these data and information to FDA if FDA asks to do so.
(name of notifier)

ToxStrategies, Inc., 739 Thornapple Drive, Naperville, IL 60540
(address of notifier or other location)

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
	Donald Schmitt, MPH; Sr. Managing Scientist	06/10/2021

SECTION G – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Form3667.pdf	Administrative
	LOACargillCarbonMonoxide2021-06-11.pdf	Administrative
	GRASNoticeCargillCarbonMonoxide2021-06-11.pdf	GRAS Notice
	AppendixACargillCarbonMonoxide2021-06-11.pdf	GRAS Notice
	Exhibit1CargillCarbonMonoxide2021-06-11.pdf	GRAS Notice