Glucose

Livestock

Identification of Petitioned Substance

Chemical Names:
D-Glucose
D-Glucopyranose
D-Glc
D-Glucopyranoside
Glc

Other Name:
Glucose
Dextrose
Corn sugar
Grape sugar

Trade Names:
Dextrose 50%
Dextrose Solution 50%
Contained in trade name products such as:
Hydra-Lyte Electrolyte Replacement
Vitamins & Electrolytes "Plus" Oral Cal MPK

CAS Numbers:
50-99-7 (D-(+)-Glucose)
2280-44-6 (D-Glucose)
54-17-1 (D-Glucose)
77938-63-7 (D-Glucose monohydrate)

Other Codes:
EINECS: 200-075-1
FDA UNII: 5SL0G7R0OK

Summary of Petitioned Use

Glucose was included in the original National Organic Program (NOP) Final Rule in December 2000 (NOP, 2000). Glucose is currently listed within the United States Department of Agriculture (USDA) organic regulations at 7 CFR §205.603(a)(13) as a synthetic substance allowed for use as a medical treatment in organic livestock production. This technical report focuses on uses for glucose in organic livestock production, primarily to treat ketosis and for use in formulated electrolyte treatments.

Glucose is one of several materials produced through the biological or chemical breakdown of starch. Each of these materials is distinguished by the degree of starch hydrolysis, as well as by name and by CAS number. The term "glucose" in this report refers to refined dextrorotatory[1] glucose (D-glucose), though it is known in the glucose syrup industry as "dextrose" (BeMiller, 2009). Dextrose monohydrate is purified, crystalline D-glucose containing one molecule of water of crystallization per molecule of D-glucose, and anhydrous dextrose is purified, crystalline D-glucose without water of crystallization (BeMiller, 2009). Commercially, the term "glucose" can also refer to glucose *syrups* (e.g., CAS# 8029-43-4) or corn syrups. These products are not the same as refined D-glucose. Glucose syrups consist of a mixture of saccharides that result from incomplete hydrolysis of starch (BeMiller, 2009; Jackson, 1995). Another product of starch hydrolysis is maltodextrin (CAS# 9050-36-6). These related materials are not considered synonymous with glucose but may be discussed at times in this technical report.

This report serves to provide technical information to complement the 1995 Technical Advisory Panel Report on glucose for the National Organic Standards Board (NOSB) to support the sunset review of glucose listed at 7 CFR §205.603(a)(13).

Characterization of Petitioned Substance

Composition of the Substance:
Glucose (also known as dextrose) is a 6-carbon (hexose) sugar molecule, and is the primary sugar in most fruits and berries (Schenck, 2000). Glucose, like most other molecules, can exist in left and right-handed versions, called enantiomers (Chemistry LibreTexts, 2015). D-glucose (subsequently referred to simply as "glucose") occurs naturally and is used by living organisms as the primary source of energy for cellular

[1] A compound is dextrorotatory when it is capable of rotating polarized light in the clockwise direction (Chang, 2000).

respiration (Murphy et al., 2014). Glucose is often found naturally as a polymerized chain in materials such as cellulose, starch, and other carbohydrates (see Figure 1, below). Glucose can bond to other glucose molecules in different orientations. Some bond orientations are referred to as "alpha" (α), while others are "beta" (β). When glucose is connected via α-1,4 bonds,[2] it forms amylose (Murphy et al., 2014). Amylopectin is formed when additional glucose molecules are attached via α-1,6 bonds (Murphy et al., 2014). These molecules are the two main components of starch (Kearsley & Dziedzic, 1995; Murphy et al., 2014; Schenck, 2000). If the hexose rings are connected through β-linkages, cellulose is the resulting polymer (Schenck, 2000).

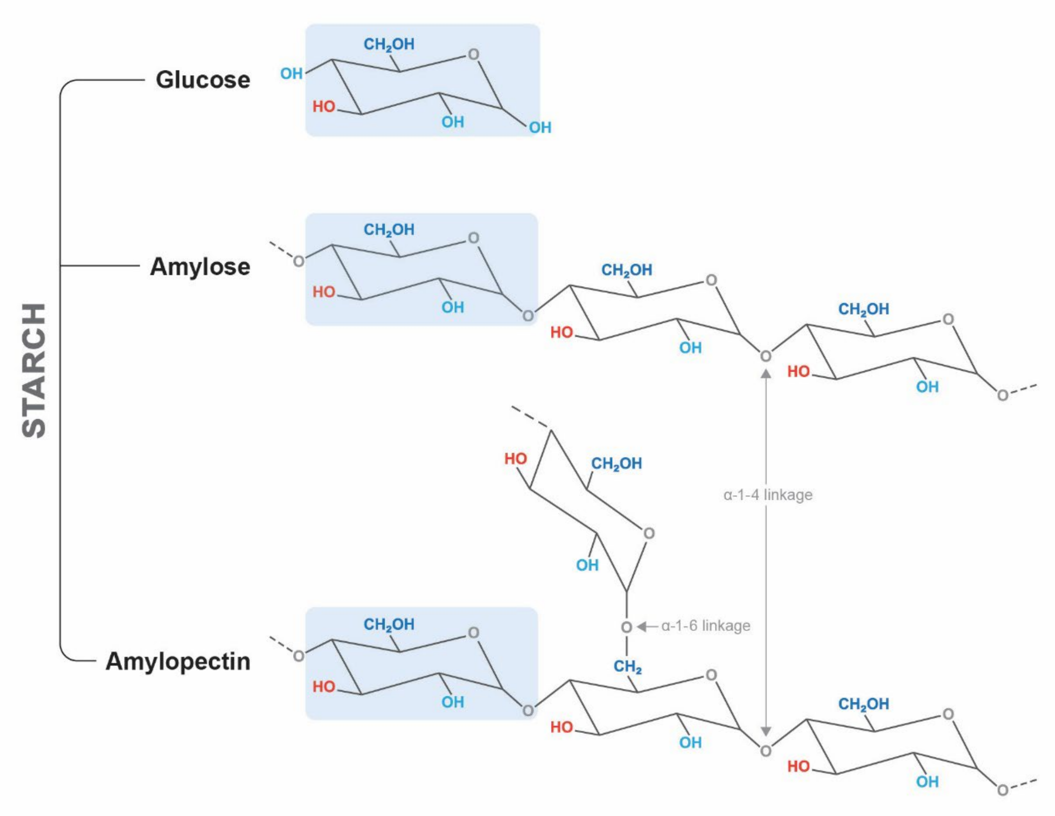

Figure 1: Chemical structure of glucose (A). Diagram also shows the two main components of starch: α-1-4 linked glucose polymers (amylose) (B) and α-1-4 and α-1-6 linked glucose polymers (amylopectin) (C). Illustration modified from Muralikrishna & Nirmala (2005).

<u>Source or Origin of the Substance:</u>

Glucose is commercially produced through the hydrolysis of starches, most commonly from maize (Jackson, 1995; Olsen, 1995; Schenck, 2000). Other sources of starch may include wheat, rice, potato, barley, sago and sorghum, depending on the global production location (Schenck, 2000; Zainab et al., 2011). The hydrolysis catalysts are typically enzymes, but also include acids (BeMiller, 2009; Jackson, 1995; Olsen, 1995; Schenck, 2000).

As mentioned, maize (*Zea mays* L.) is the major starch source worldwide, representing about 85% of worldwide starch production (R. Zhang et al., 2021). United States is the biggest corn producer worldwide, with a productive volume of over 345 million metric tons in 2019 (Shahbandeh, 2021). In the United States, the production of glucose from corn starch increased from 483,000 tons in 1964 to 642,000 tons in 1992 and reached 713,000 tons in 2019 (USDA-Economic Research Service, 2020).

[2] A bond is called "α-1,4 bond" when the α-hydroxyl functional group (-OH *below* the glucose ring) of the Carbon 1 (C1) of a glucose molecule bonds the α-hydroxyl functional group of the Carbon 4 (C4) of another glucose molecule, producing water and creating an O-glyosidic (oxygen mediated) link.

The degree of hydrolysis of the starch is commonly defined as the dextrose equivalent (DE). Complete hydrolysis of starch gives nearly pure glucose syrups or liquors. Crystalline glucose is produced from these highly refined glucose (94-95%+) liquors (BeMiller, 2009; Schenck, 2000). The liquor is refined by adsorption-separation chromatography,[3] demineralization, evaporation and then finally crystallization to obtain either anhydrous dextrose (D-glucose) or dextrose monohydrate (D-glucose monohydrate) (BeMiller, 2009), both of which are referred to as 'glucose' throughout this report.

See *Evaluation Question #2* for details regarding specific glucose manufacturing processes.

Properties of the Substance:

Glucose is odorless and sweet, and soluble or miscible with water (National Center of Biotechnology, 2021). Glucose injectable solutions are available at different concentrations (e.g. 5%-50% glucose anhydrous and/or glucose monohydrate) (FDA, 2021). Table 1 summarizes some of the chemical and physical properties of glucose.

Table 1: Properties of glucose

Property	**Value**
Physical State and Appearance	Crystalline powder (*a*-D-Glucose)[b]
Odor	Odorless[a]
Taste	Sweet[a]
Color	White[a]
Molecular Formula	$C_6H_{12}O_6$[b]
Molecular Weight	180.16[b]
Specific Gravity	1.56[b]
pH	A 0.5 molar aqueous solution = 5.9 [b]
Solubility	Soluble[b]
pKa	12.92 at 0 °C[b]
Boiling Point	Greater than 212 °F at 760 mm Hg[b]
Melting Point	Less than 32 °F[b]
Critical Temperature	755 deg K (est)[b]
Vapor Pressure	8.0 x 10^{-14} mm Hg at 25 °C /extrapolated from a higher solid-phase temperature range[b]
Stability	Stable under proper storage conditions[b]
Reactivity	Weak reducing agent[b]

Source: a=(Schenck, 2000; Wilson et al., 1995), b=(National Center of Biotechnology, 2021)

Specific Uses of the Substance:

Glucose, in solution and in its crystalline form, is primarily used for food and pharmaceutical purposes in the United States (Hull, 2010; Jackson, 1995; Macrae et al., 1993; Schenck, 2006). Glucose is used to treat

[3] Adsorption-separation chromatography is a technology used to separate two substances using the different affinity they have for a resin. When a sample passes through columns that contain the resin, the rate of diffusion of the components causes them to separate as they flow through it (Coskun, 2016; Purolite, 2021).

metabolic disorders such as hypoglycemia[4] (National Center of Biotechnology, 2021), as a component of certain products (e.g., electrolytes) and as an excipient (e.g., as a binder in oral tablets).

Glucose is included at §205.603(a)(13) without annotation where its use is only restricted to medical treatments (as well as preventive management standards per 7 CFR §205.238). While it is allowed for livestock medical treatments beyond ketosis and dehydration, these two uses of the substance are the most common. Glucose is also a common component of electrolyte formulations, and is used as an excipient in livestock health care treatments

Ketosis treatment
One of the primary uses of glucose in organic production is in the treatment of ketosis in ruminants. Ketosis is a metabolic disease that can occur shortly after parturition (labor and delivery) in ruminants due to an energy imbalance[5] related to the sudden onset of milk production (Duffield, 2000; Herdt, 2000). It is fatal if untreated. Subclinical ketosis is defined as an increase of ketone bodies[6] in the blood, urine, or milk, in absence of obvious clinical signs of disease (G. Zhang & Ametaj, 2020). Its primary feature is elevated levels of ketones in the animal's blood stream (Andersson, 1988; Duffield, 2000). Clinical ketosis also presents elevated levels of ketones; in addition it includes loss of appetite, decreased milk production, and loss of body condition (David Baird, 1982; Herdt, 2000). Both clinical and subclinical ketosis are also associated with increased levels of non-esterified fatty acids (NEFA) and decreased levels of blood glucose (Herdt, 2000; Mann et al., 2017). The hypoglycemic hypothesis states that alterations of glucose and lipid metabolism are associated with the development of ketosis, decreased level of glucose being one of the major changes in affected animals (G. Zhang & Ametaj, 2020). Hypoglycemia can occur when the liver is not able to produce enough glucose to meet the demands of the postpartum ruminant. Low concentrations of blood glucose are associated with low concentrations of insulin (hypoinsulinemia), which triggers the mobilization of fatty acids from adipose tissue (lipolysis), thereby increasing ketone body formation (G. Zhang & Ametaj, 2020). Excessive lipolysis can lead to ketosis (G. Zhang & Ametaj, 2020). Ketosis can be monitored by measuring the amount of β-hydroxybutyrate (BHB), a ketone containing molecule, in the animal's blood (Gerloff, 2000; Gordon et al., 2013). Glucose is often given to ruminants through an intravenous injection to replace the depleted, naturally occurring blood glucose. The replacement glucose serves as an energy supplement when the animal experiences negative energy balance and the nutritional demand of producing milk outstrips the dry matter intake the animal consumes (Herdt, 2000; Mann et al., 2017).

Ketosis is also discussed in detail within the 2021 *Propylene Glycol* Technical Report (USDA, 2021).

Neonatal hypoglycemia treatment
Immature neonates and neonate ruminants can become hypoglycemic because of underdeveloped gluconeogenic mechanisms, if they do not ingest adequate amounts of colostrum and milk (Klein et al., 2002). In cases of neonatal hypoglycemia, the immediate treatment consists of the intravenous or intraperitoneal administration of a glucose solution. Under-nurtured neonatal calves and immunosuppressed animals are predisposed to coliseptisemia (invasion of the blood stream by coliform bacteria). Animals affected by this disease are usually treated by the intravenous administration of large volumes of balanced electrolyte solutions over several hours; fluids should include glucose to correct hypoglycemia (Walter, 2020).

Formulated oral electrolyte solutions and rehydration therapies
Glucose helps facilitate sodium transport within the intestines (Naylor, 1990). Because of this, it is a key ingredient in oral rehydration therapies to treat dehydration in young ruminants. Calves, lambs, kids, and swine are most likely to benefit from oral electrolyte solutions. Neonatal diarrhea (scours) remains the most common cause of death in beef and dairy calves (Smith, 2009). Young livestock often experience

[4] An abnormally diminished content of glucose in the blood (Rozance & Hay, 2010).
[5] An imbalance between the energy that enters into the body as feed (dry-matter intake) and the energy that is released from the body in the form of milk (G. Zhang & Ametaj, 2020).
[6] ketone bodies are hydroxybutyrate (OHB), acetoacetate (AcAc), and acetone (Ac) and can be found in the blood, urine, and milk of cows in ketosis (G. Zhang & Ametaj, 2020).

dehydration due to diarrhea following an infection by *E. coli* or cryptosporidium (Naylor, 1999). This causes the animals to expel (rather than absorb) the large amounts of fluid that is secreted in the small intestine. Regardless of the pathogen and mechanism involved, diarrhea increases the loss of electrolytes and water in the feces of calves, and decreases milk intake, resulting in dehydration and negative energy balance (Smith, 2009). Diarrhea is by far the most common indication for fluid therapy in neonatal calves. Oral electrolyte solutions have classically been used to replace fluid losses, correct acid-base and electrolyte abnormalities, and provide nutritional support (Smith, 2009).

Oral electrolyte solutions were developed in the twentieth century as a treatment for cholera infections. The original World Health Organization (WHO) electrolyte was based on a formulation that contained an approximately equimolar mixture of sodium (990 mmol/ L) and glucose (2%), potassium, glycine and bicarbonate (Smith, 2009). Although much research has been done on oral fluid therapy since that time, the formulation of oral fluids has not moved far from the original (Smith, 2009). Commonly recommended oral rehydration solutions contain 75 mmol to 139 mmol/L of glucose (Reid & Losek, 2009).

Excipient

Glucose is a common excipient ingredient in livestock health care products (OMRI, 2021), and meets the annotation for excipients used in drugs and biologics used to treat organic livestock at §205.603(f)(1).

Other uses

As an ingredient, glucose is generally recognized as safe (GRAS) by the U.S. FDA (21 CFR 184.1857) without limitation when used in food. Glucose monohydrate (usually referred to as dextrose monohydrate) is highly valued as an ingredient in confectionery applications (Jackson, 1995). It is important for preserves. At any given concentration, a dextrose solution contains almost twice as many dissolved molecules as a sucrose solution, and therefore a solution of glucose exerts a greater osmotic pressure than a sucrose solution (Jackson, 1995), aiding with the osmotic dehydration. Glucose is also a valuable ingredient in powdered sherbet centers, lemonade powders, chewing gum, compressed tablets and fondant (Jackson, 1995). It is also sometimes used in brewing (Schenck, 2000).

Glucose is used in the production of microbially-derived products, such as citric, lactic, and acetic acids, as well as enzymes, vitamin C, and antibiotics (Schenck, 2000). It is also used in producing fuel ethanol, plastics, insulating foam, and adhesives (Schenck, 2000). Glucose is used in conventional livestock feeds as an appetite stimulant due to its sweet flavor (Precision Feed Technologies, LLC, 2021; Stock Show Secrets, 2022; Aspen Veterinary Resources, Ltd., 2021)..

Anhydrous glucose (anhydrous dextrose) is used for intravenous injections in humans for various pharmaceutical and medicinal preparation (Fellers, 1939). In the pharmaceutical industry, glucose is found as both an active ingredient, and as an excipient (inactive ingredient). Glucose injectable solutions are used as a source of water and calories for patients that required intravenous nutrition (FDA, 2021). As an excipient, glucose has widespread use as a sweetener, reducing agent, bulking agent and soluble carrier for an active pharmaceutical ingredient (Srivastava et al., 2016).

Approved Legal Uses of the Substance:

Food and Drug Administration (FDA)

D-glucose appears in the "Corn sugar" listing at 21 CFR 184.1857. It is considered a substance that, when added directly to human food, is generally recognized as safe (GRAS). Glucose sirup (also spelled "syrup") is found under the "Corn Syrup" listing (21 CFR 184.1865) and under the sweeteners and table sirups section (21 CFR 168.120). Corn sugar and corn syrup are allowed as food ingredients with no limitation other than current good manufacturing practice; glucose syrup is allowed also as a sweetener and table syrup (21 CFR 168.120).

Environmental Protection Agency (EPA)

Dextrose and corn syrup appear on the 2004 EPA List 4A as inert ingredients of minimal risk (USA EPA, 2004). "D-glucose," "Corn syrup" and "syrups, corn, dehydrated" are also considered to fall under the category of "commodity inert", and are therefore approved for food and non-food pesticidal use as inerts (US EPA, 2004).

Action of the Substance:

Hypoglycemia and ketosis treatment

When delivered intravenously, glucose provides an immediate supply of sugars to the blood stream and effectively treats nervous ketosis,[7] the most severe form of the disease (Gordon et al., 2013). Because glucose is immediately bioavailable to ruminants, its effects are not long-lasting (Wagner & Schimek, 2010). Glucose provides less than 12 hours of suppression of BHB, a ketone often used as a marker for ketosis, and only one treatment of 500 mL or 1 L of 50 percent glucose is unlikely to prevent or resolve ketosis in a dairy cow (Wagner & Schimek, 2010). Dairy cows may need follow-up treatment when using glucose because each dose is effective for less than 12 hours (Herdt & Emery, 1992). Oral administration of glucose to sheep is possible, but research suggests that sheep may not successfully absorb the needed amount of glucose through their rumen (Sargison, 2007).

Gordon et al. 2013 observes that dextrose (glucose) should be considered a second-line treatment for cases of ketosis. The treatment with dextrose should be used in animals with severe ketonemia and concurrent hypoglycemia suffering from nervous signs (abnormal licking, chewing on pipes or concrete, gait abnormalities, and aggression). These animals should then receive additional other treatments for longer-term effectiveness (Gordon et al., 2013).

Dehydration treatment

Glucose can be co-transported with sodium from the intestinal lumen to the inside of the enterocyte at the brush border membrane (special epithelium found in some tissues, like the intestine) (Smith, 2009). At the basolateral membrane, specific transmembrane enzymes actively pump sodium ions out of the cell, thus raising the intercellular osmolality (Smith, 2009). This increase in intercellular osmolality then draws more water from the intestinal lumen through the tight junctions between cells, thereby expanding extracellular fluid volume and rehydrating the animal (Smith, 2009).

Combinations of the Substance:

Glucose is commercially available in two forms—in diluted liquid solutions and in a crystalline powder. Some products contain hydrochloric acid or sodium hydroxide for pH adjustment (VetOne®, 2022). Aside from that, intravenous dextrose (glucose) is formulated with sterile water.

In the case of oral electrolytes, some products may be formulated with glucose, certain salts in the form of ions – sodium, potassium, chloride, acetate, citrate, etc., and amino acids to aid with the hydration process. Sometimes preservatives like citric acid or propionic acid are included as part of the formulation. Other substances may be added to enrich products and improve the nutritional intake of the treated livestock. For example, some products may be enriched with vitamins, microorganisms, and/or amino acids like glycine (Agri Laboratories, Ltd., 2022). Whether amino acids are needed in addition to glucose in oral electrolyte solutions is not well understood; however, the addition of glycine does seem to further improve water absorption in the intestine (Smith, 2009).

Status

Historic Use:

Ketosis treatment

Ketosis as a disorder in cattle has been known since at least 1849 (McSherryt et al., 1960). In 1928, Hupka noted that administering glucose helped alleviate symptoms of ketosis (McSherryt et al., 1960). Since the 1930s, glucose has been considered a staple to treat hypoglycemia associated with ketosis (Gordon et al., 2013).

[7] Nervous ketosis is marked by signs that may include excitement and hyperesthesia, depraved chewing and licking (occasionally with self-mutilation), or abnormal gait (including hypermetria or ataxia) (Gerloff, 2000).

Glucose was studied extensively in the 1940s and 1950s, but researchers relied on studies where all affected animals were given the same treatment, and no controls were used for comparison (Gordon et al., 2013). According to Gordon et al., as of 2013, glucose has never been studied in a randomized clinical trial to determine efficacy as a standard treatment for ketosis.

Mann et al. (2013) found that treating cattle with a combination of glucose and propylene glycol reduced BHB more than either substance alone. Capel et al. (2021) also investigated the effect of intravenous glucose treatment combined with oral propylene glycol therapy on the resolution of lactating cow's hyperketonemia by assessing the levels of blood BHB. In contrast to what Mann et al. found, the addition of glucose for 1 to 3 days provided no improvement in resolution of ketosis.

Dehydration treatment

Oral electrolyte solutions became widely commercially available in the early 1970s and gained rapid acceptance in the treatment of diarrheic animals (Naylor, 1990). Oral electrolytes continue to be the hallmark of routine therapy for treating neonatal calf diarrhea (Smith, 2009). Glucose is present in various concentrations in virtually all commercially available oral electrolyte solutions (Smith, 2009). In addition to the treatment of sick neonatal calves, fluids and electrolytes are used in sick ruminants to correct imbalances of acid-base, electrolyte, or water, and to optimize tissue blood flow, provide nutrients, or treat shock (Constable, 2003).

Organic Foods Production Act, USDA Final Rule:

The NOSB recommended including glucose on the National List in 1995 as a synthetic material allowed for use in livestock medical treatments. The National Organic Program currently allows glucose at 7 CFR §205.603(a)(13) for use as a disinfectant, sanitizer, and medical treatment as applicable. As a medical treatment, glucose is limited to use after the onset of illness by 7 CFR 205.238(c)(2).

International

Canadian General Standards Board Permitted Substances List

The Canadian General Standards Board includes glucose on CAN/CGSB 32.311-2020 Table 5.3 (Health Care Products and Production Aids) without annotation. Table 5.3 also includes a listing for "Formulants (inerts, excipients)," allowing glucose to be used as an excipient ingredient with a permitted active ingredient. CAN/CGSB 32.310-2020 6.6.2 prohibits the use of veterinary drugs in the absence of illness.

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999)

The CODEX guidelines state in Annex 1, Part B "Health Care" that producers must first prevent disease through the selection of appropriate breeds, use of high-quality feed, and access to pasture and exercise, among other preventive principles. If these management practices are not enough to prevent disease, a producer may use allopathic[8] veterinary drugs if phytotherapeutic products are ineffective. Glucose is not explicitly mentioned as a health care substance, but it is included in allopathic veterinary drugs and therefore allowed based on the definition at Section 2.2 of the guidelines.

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008

Title II, Chapter 2, Section 4 of the EC No. 889/2008 focuses on disease prevention and veterinary treatment. Article 24, paragraph 3 requires producers to use preventive measure to ensure animal health, and also allows producers to use veterinary medicinal products if prevention or phytotherapeutic products fail. Glucose is included in veterinary medicinal products, and therefore would be allowed under EEC regulations. Article 24, paragraph 5 requires that organically produced foodstuffs from treated animals be withheld from the stream of commerce for twice the legal withdrawal period or at least 48 hours.

Japan Agricultural Standard (JAS) for Organic Production

[8] Allopathy was coined in 1810 by German physician Samuel Hahmann to designate the usual (western) practice of medicine. Allopathic medicine focuses on signs and symptoms of the diseases, identifying the pathology behind the disease and treating them with drugs, surgery, etc. (Parajuli & Sanjib, 2021).

Article 4 of the Japanese Agricultural Standard for Organic Livestock includes the "Health control" section, specifying practices for organic livestock production. The standard requires that producers implement preventive practices before using veterinary drugs, and veterinary drugs may only be used for therapeutic purposes. Again, glucose is included within veterinary drugs and may therefore be allowed under the JAS. A withdrawal period is noted. It must be 48 hours from the last administration of drugs to slaughter for foods, milking, and egg collection, or twice the period of drug withdrawal defined by Articles 14-1, 9, 4, and 6 of the Pharmaceutical Law for the approval of drugs, change of approvals, reexamination of drugs, and drug efficacy review, whichever is longer.

IFOAM – Organics International

Section 5.6 of the IFOAM Standard for Organic Production and Processing describes the requirements for the use of veterinary medicine in organic livestock production. Section 5.6.1 requires that producers establish preventive practices, including good quality feed and access to the outdoors, to avoid illness in their livestock before using synthetic allopathic veterinary medical products. Glucose, when used to address dehydration and ketosis symptoms in livestock, would be considered a synthetic allopathic veterinary medical product, and Exception (c) would allow its use under veterinary supervision with a minimum withdrawal period of at least 14 days. Prophylactic use of synthetic allopathic veterinary drugs is prohibited.

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?

(A) Glucose is used as an active ingredient in livestock medicines.
(B) Glucose is a 2004 EPA List 4A inert ingredient of minimal risk (US EPA, 2004). Furthermore, dextrose (D-glucose; CAS No. 50-99-7) and dextrose monohydrate (D-glucose monohydrate; CAS No. 77938-63-7) are also considered "commodity inerts" that are exempt from the requirement of a tolerance at 40 CFR §180.950(a)(i) (US EPA, 2020).

Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

Manufacturers produce glucose using these basic chemical and physical steps: hydrolysis, clarification, color removal, evaporation, and crystallization (for crystalline dextrose, or glucose, production). Currently, manufacturers produce crystalline glucose products from acid-enzyme and enzyme-hydrolyzed glucose syrups (Schenck, 2000). In the past, glucose was obtained from acid-hydrolyzed syrups.

Corn starch slurry obtained through the wet milling process is usually the starting material for glucose production. The pH of the starch slurry is adjusted to 6.0 and calcium ions (usually in the form of calcium chloride) may be added in order to stabilize or improve the efficiency of the enzymes (Schenck, 2000).

When preparing the initial starch slurry, sulfur dioxide may be added in order to minimize bacterial colonization and to block the Maillard reaction (the reaction of proteins with reducing sugars, which produces colors) (Hull, 2010).

Enzymatic hydrolysis:
Using the enzymatic hydrolysis process, starch is hydrolyzed by the addition of high-temperature stable enzymes. Using direct steam injection or some other method, the starch slurry with enzymes is heated to approximately 105 °C in order to liquefy it (Schenck, 2000). The pH and other conditions might be readjusted, and more enzyme(s) may be added for starch hydrolysis (saccharification) (Hull, 2010; Macrae et al., 1993; Olsen, 1995).

To process starch into glucose, four main type of enzymes are used: α-amylase, ß-amylase, glucoamylase and pullulanase (BeMiller, 2009). The enzyme α-amylase is one of the most important enzymes used in the food industry, and these enzymes account for approximately 25% of the world enzyme market (de Souza & Oliveira Magalhães, 2010). They hydrolyze the α-1,4-glycosidic linkages of the starch polysaccharide. Thermostable (heat-stable) α–amylases are desirable because liquefaction and saccharification of starch are performed at high temperatures (de Souza & Oliveira Magalhães, 2010; Hull, 2010; Reddy et al., 2003).

Industrially, saccharification is predominantly carried out by α-amylases from *Bacillus amyloliquefaciens*, *Bacillus licheniformis*, or *Bacillus stearothermophilus* (Bilal & Iqbal, 2020). The commercial α-amylases are produced by fermentations of genetically modified bacteria, where the native gene has been manipulated to code for an enzyme with improved performance characteristics, such as heat stability (Nielsen, 2012; University of Reading NCBE, 2018; DuPont Industrial Biosciences, 2015; Olempska-Beer, 2004; Silano et al., 2018).

Acid hydrolysis:
Acid hydrolysis may be used to partially hydrolyze the starch slurry before further enzyme hydrolysis, as well as to make 35 and 42 DE (dextrose equivalent) finished glucose syrups. In the acid conversion process, a starch slurry is acidified (usually with hydrochloric acid) to a pH of about 2 and pumped to a vessel where it is heated and pressurized. This process partially hydrolyzes the starch slurry. After hydrolysis, the slurry is neutralized (usually with sodium carbonate) to a pH 4.5-4.8, which causes proteins and lipids to precipitate.

When the end product is a glucose syrup, the slurry is then purified by centrifugation, skimming and/or passing through deep tanks to remove impurities (solids, fats, proteins, oils and fine fibers), and then filtered. The product is clarified using granular activated carbon to further remove impurities, and then concentrated by evaporation. The resulting syrup is polished through further clarification and decolorization. Finally, the syrup is concentrated again in evaporators to the final required density. Some syrups are treated with ion exchange resins for further refinement (Hull, 2010; Macrae et al., 1993; Mironescu & Mironescu, 2006).

Acid–enzyme process:
The combination of acid and enzymes is used to produce high glucose syrups such as D.95 (95% glucose). The starch slurry is only partially converted by acid to a given DE The temperature and acidity of the slurry are adjusted to the optimal conditions required by the specific enzyme or enzymes to be used during the saccharification process, where the starch is broken down into monosaccharides. The DE is monitored and the conversion processes stopped when the desired sugar composition is reached. The syrup is centrifuged, filtered, clarified with activated carbon and ion exchange treatment, polished, and evaporated as needed (Hull, 2010; Macrae et al., 1993; Olsen, 1995). Glucoamylase (also known as amyloglucosidase or AMG) is used after the acid hydrolysis and the conversion is mediated by α-amylase (Hull, 2010).

Purification:
Glucose monohydrate crystals are produced through the crystallization of 95 DE syrups inside crystallizers (large horizontal, cylindrical batch tanks) (BeMiller, 2009). Inside these tanks, the syrup is cooled to achieve

the proper level of supersaturation (temperature and concentration conditions required for the crystals to precipitate), and subsequently to achieve the crystallization of glucose in its monohydrated form (BeMiller, 2009). The crop of crystals is then washed and centrifuged in basket centrifuges to remove the remaining liquor, which may be reprocessed to yield a second crop of crystals (BeMiller, 2009). Crystals are then dried with a stream of hot air, cooled, and stored. Throughout this purification process a product containing 99.9% dextrose can be obtained (Hull, 2010). Anhydrous dextrose is produced by dissolving the monohydrate in hot purified water and refining it again (BeMiller, 2009).

During the purification and crystallization steps to make glucose, the enzymes are typically removed. Absence of the α-amylase protein in the final (purified) sweetener syrup has been confirmed experimentally (Pronk & Leclercq, 2004). In addition, governmental and international organizations such as the FDA and the World Health Organization (WHO) through the International Program on Chemical Safety (IPCS) have observed that these enzymes are GRAS and Allowable Daily Intake (ADI) not specified, respectively (Pronk & Leclercq, 2004).

<u>Evaluation Question #3:</u> Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Glucose is produced naturally through photosynthesis and is stored in plants in the form of starch, a polymer made from glucose. Current industrial processes use a combination of biological, chemical and physical tools to obtain purified glucose. These processes yield products that can be ≥99.5% pure.

Glucose is classified[9] as a synthetic substance when acid hydrolysis and acid/enzyme hydrolysis are used in the production, but as a nonsynthetic material when the production is achieved through enzyme hydrolysis.

Commercially available products using glucose can be formulated with synthetic substances. Some products such as intravenous dextrose solutions are diluted in water to achieved desired concentrations. These injectable solutions may contain hydrochloric acid or sodium hydroxide for pH adjustment. In the case of oral electrolytes, these types of products may be formulated with glucose, certain salts in the form of ions – sodium, magnesium, etc., and amino acids to aid with the hydration process, and sometimes preservatives like citric acid or propionic acid are included as part of the formulation.

<u>Evaluation Question #4:</u> Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

Glucose and glucose-containing compounds are naturally abundant in the environment. Generally speaking, sugars such as glucose are the most abundant organic compounds in the biosphere because they are the basic components of all polysaccharides (chitin, cellulose, hemicellulose, starch, pectin, etc.) (Gunina & Kuzyakov, 2015).

Glucose is an easily metabolized substance (Brosnan, 1999; Murphy et al., 2014). Its use as an animal drug is not expected to contribute to significant quantities in the environment. However, when glucose is given to animals, some may be excreted in urine. For example, when glucose was given intravenously to healthy cows, 13 to 26% of the glucose was excreted in the urine, depending on the total quantity given (Metzner et al., 1993). Soil systems with active microbes should easily consume these amounts of glucose (in a matter of hours to days, depending in the type of soil) if present in the excreted urine of treated animals as shown by the studies performed by Ferreira et al. 2013, Padmanabhan et al. 2003 and Gunina et al. 2015. For more information regarding these studies, refer to *Evaluation Question #8*.

[9] Considering the Decision Tree for Classification of Materials as Synthetic or Nonsynthetic in NOP Guidance 5033-1,

<u>Evaluation Question #5:</u> Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

Glucose is an important biomolecule that has very low toxicity. According to several safety data sheets, the oral LD_{50} in rats is 25800 mg/kg (DHI Milieu Ltd., 2008; Fisher Science Education, 2015; Hach Company, 2005). When glucose is metabolized through aerobic respiration, the breakdown products are water and CO_2 (Murphy et al., 2014). Plants and cyanobacteria recycle CO_2 and water back into glucose via photosynthesis (Galant et al., 2015). Glucose typically persists in the environment within polymers such as chitin and cellulose (Gunina & Kuzyakov, 2015).

<u>Evaluation Question #6:</u> Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

The major environmental impacts associated with the production of starch, from which glucose is derived, occur during the agricultural stages that produce the starch-containing material used for glucose production (e.g., potato, maize, wheat, and cassava) (Blanco-Cejas et al., 2020). The agricultural stages usually involve intensive consumption of natural resources such as land occupation and transformation, use of fertilizers and pesticides, depletion of fossil fuels for machinery, etc. (Blanco-Cejas et al., 2020).

The results of a life cycle assessment[10] (LCA) for glucose ascribe 60-96% of the generated impact to the production of the starch (Blanco-Cejas et al., 2020). Previous studies noted that 70% of the environmental footprint of glucose production is generated by the starch manufacture (Blanco-Cejas et al., 2020).

The impact to produce 1000 kg of glucose from corn (100% DM) was quantified by Renoulf et al. (2008) at 6000 MJ of energy input; 1000 kg CO_{2eq} for global warming; 8.5 kg SO_{4eq} for acidification and 2.8 kg PO_{4eq} for eutrophication potential (Kis et al., 2019; Renouf et al., 2008). By comparison, Renoulf et al. (2008) note that glucose from sugar cane is more sustainable than corn-derived glucose in terms of energy input, greenhouse gas emissions and possibly acidification potential. Kis et al. 2019 noted that inverted liquid sugar has lower carbon and water footprints than glucose and fructose syrups and derivatives (by 38% and 95%, respectively), and its production requires less fossil energy (by 31%) and less agricultural land (by 67%). After evaluating an LCA for EU starch manufacturing plants, Vercalsteren et al. (2012) noted that the starch industry typically causes little waste production because all side streams are used to produce useful products that have an economic value; waste sent to landfill or incineration is almost nonexistent. Glucose is one of the side stream products of the starch industry and, as a livestock medical treatment, it is unlikely to contaminate the environment. Contamination related to the disposal of this product represents a negligible risk to the environment.

<u>Evaluation Question #7:</u> Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

Glucose may interact aggressively with strong oxidizing agents and can produce toxic gases when combusted (Hach Company, 2005), however these reactions are unlikely to happen in the utility context of livestock medicine. For environmental effects that the glucose may have, please review *Evaluation Question #4*. For human health and glucose metabolism, please review *Evaluation Question #3*. Glucose is unlikely to cause serious damage to producers.

<u>Evaluation Question #8:</u> Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).

[10] A life cycle assessment (LCA) is a method to analyze the environmental impacts of a product. An LCA quantifies the potential environmental effects of a product over its entire life cycle, meaning that the extraction of raw materials, the production of the materials and the product, the use and the end-of-life treatment are taken into account (Vercalsteren et al., 2012).

Glucose is a universal fuel for cellular metabolism. Glucose in the environment is captured rapidly by microbes where it is used for maintenance and growth (Gunina & Kuzyakov, 2015). Glucose addition to the soil has been utilized as a strategy for measuring the respiratory response of the soil microbial community (Ferreira et al., 2013). Glucose labeled ^{14}C and ^{13}C are often used to perform biodegradation assays that measure the microbial activity of water and soil samples. Soil microbes can mineralize[11] glucose added to the soil (at 7 percent) within the first 8 hours of exposure (Padmanabhan et al., 2003).

Gunina & Kuzyakov (2015) estimated the sugar C mineralization to CO_2 using a literature review of 74 data points collected from 16 studies on glucose ^{14}C or ^{13}C decomposition within the first 24 h after its addition into the soil. The calculations performed showed that the estimated maximum glucose C decomposition rate to CO_2 was 1.1 percent min^{-1} (Gunina & Kuzyakov, 2015). At this high rate, half of the glucose C should be mineralized to CO_2 within the first hour (Gunina & Kuzyakov, 2015). This study also shows that the time of glucose duration as a whole molecule during microbial metabolization is much shorter that 30 min (Gunina & Kuzyakov, 2015).

Ferreria et al. (2013) demonstrated that soil systems with no tillage use more carbon than systems with tillage, and that the microbes in these kinds of systems can consume up to 2000 mg of glucose kg^{-1} dry soil after 24 h of incubation.

In aquatic environments, glucose alone can support 20-30 percent of bacterial production in some oceanic regimes and, as observed, in one Danish lake (Kirchman, 2003). In the Gulf of Mexico, Antarctic seas, and in two Swedish lakes, glucose accounted for <10% of bacterial growth (Kirchman, 2003). In the surface waters of the Gulf of Mexico, glucose was found at a concentration of 2-15 nmol/L (Skoog et al., 1999). Gocke et al. (2003) found that turnover rates of glucose were very fast in highly productive lagoons: less than 20 minutes. In less productive systems, the cycling of glucose had a turnover time of two hours (Gocke et al., 2003).

Considering the studies above, it is possible to conclude that glucose given to cows intravenously, as a component of an electrolyte treatment, or as an excipient in other medical products, does not represent a threat to water and soil systems. The glucose that is not metabolized might be excreted in the urine of the treated animals, and the concentrations would be small enough that soil systems with active microbes should easily consume these amounts of glucose in a matter of hours to days depending in the type of soil.

<u>Evaluation Question #9:</u> Discuss and summarize findings on whether the use of the petitioned substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

As a substance that is critical to the metabolism of living cells, glucose is naturally pervasive in the environment (Brosnan, 1999; Gunina & Kuzyakov, 2015). The use of glucose as intended at 7 CFR §205.603(a)(13) by organic livestock producers is therefore unlikely to cause harm to the environment. Manufacturing glucose does have the potential to cause environmental damage. The major environmental impact of glucose production is associated with the agricultural production of the starch-containing produce (corn, wheat, potato, etc.) (Blanco-Cejas et al., 2020; Kis et al., 2019; Vercalsteren et al., 2012). About 70-96% of the ecological impact of glucose manufacturing is caused during the starch production (Blanco-Cejas et al., 2020). However, if designed optimally, starch production plants should cause little waste production because all the side streams can be used to produce economically valued products (Vercalsteren et al., 2012).

As described in previous sections, glucose is a universal energy source for living organisms. It is not acutely toxic for animals, and almost any organism easily metabolizes it. Microorganisms in water and soil decompose glucose into CO_2 and water. Plants and cyanobacteria take CO_2 and water and produce glucose

[11] The term mineralization is often used in microbial respiration studies and it describes the degradation of a compound to its "mineral components" (i.e. carbon dioxide and water) and is synonymous with ultimate biodegradation or complete biodegradation (Knapp & Bromley-Challoner, 2003).

and other carbohydrates like starch, cellulose, and chitin through photosynthesis, closing the biogeochemical cycle.

Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

High levels of glucose in the blood for a persistent period (hyperglycemia) can have a toxic effect on cells, tissues and organ systems (Giri et al., 2018). Insulin, secreted from the pancreatic β cells, is a key element in the homeostatic regulation of blood glucose levels (Fujii et al., 2019). A prolonged hyperglycemic condition leads to severe diabetic condition by damaging the pancreatic β-cell and inducing insulin resistance (Giri et al., 2018). People suffering from diabetes or prediabetes have a reduced ability to tolerate glucose loads, and therefore their health could be negatively affected if they were to receive intravenous glucose treatment unpaired with an insulin treatment (Dagogo-Jack & Alberti, 2002). Glucose as a component of livestock health care products does not represent a health risk for the producers because they would not be ingesting the substance. In addition, the glucose that is not metabolized by the animal will not persist in the dairy products or meat, as it is excreted in the urine (Metzner et al., 1993).

Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

Glucose

Glucose production utilizing solely the enzyme hydrolysis process (Refer to *Evaluation Question #2* for further information) would yield a nonsynthetic product per NOP 5033-1 “Guidance: Decision Tree for Classification for Materials as Synthetic or Nonsynthetic”.

Molasses

Molasses is a nonsynthetic, agricultural commodity commonly added to livestock feed. Adding molasses as a top-dressing to forage (or fed directly as a fluid) can be used pre-partum as a preventive measure, and as a treatment for subclinical ketosis postpartum (Havekes et al., 2020; Lans et al., 2007). For more information, review *Evaluation Question #11* of the 2021 Propylene Glycol Technical Report (2021).

Glycerin

Nonsynthetic glycerin, or glycerol, can be used for the treatment of ketosis. It can be delivered either as an oral drench or combined in the feed ration. Glycerin can be of special benefit to treat ketosis in sheep (Cal-Pereyra et al., 2015; Ferraro et al., 2016; Kalyesubula et al., 2019). High dosages of glycerin may have negative impacts on biodiversity in the rumen, and work remains to clarify rumen impact of glycerin use (Kupczyński et al., 2020).

Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Ketosis:

Several studies have found that animals that are given the opportunity to graze and eat high-forage diets have a decreased incidence of ketosis (Richert et al., 2013; Vickers et al., 2013). There is evidence that organic cows, required to obtain 30 percent of the daily matter intake (DMI) from grazing, are one third less likely to have ketosis than conventional animals (Hardeng & Edge, 2001). Grazing animals, both cows and sheep, also produce milk and meat that is higher in omega-3 fatty acids (Daley et al., 2010; Nuernberg et al., 2005; Wyss et al., 2010). There is evidence that omega-3 fatty acids improve energy metabolism immediately after calving (Grossi et al., 2013), suggesting that animals who graze may be less likely to succumb to ketosis.

Higher levels of neutral detergent fibers (the insoluble fibers in animal feed such as cellulose, hemicellulose, and lignin) in feed are correlated with lower levels of serum NEFA (Litherland et al., 2013; Van Soest et al., 1991). Lower levels of serum NEFA are negatively correlated with subclinical and clinical ketosis in cows (Drackley & Cardoso, 2014; Duffield, 2000; Herdt, 2000; Vanholder et al., 2015). Litherland et al. (2013) found that increased amounts of wheat straw in a pre- and postpartum diet in dairy cows resulted in lower postpartum serum NEFA, suggesting healthier metabolism in postpartum cows. The wheat straw helps to moderate the prepartum energy intake for animals. Animals overfed with energy prepartum experienced a negative energy balance for longer into their lactation, which is the primary driver of postpartum ketosis (Litherland et al., 2013). High-energy diets are typically low in both neutral detergent fibers and acid detergent fibers, and are therefore nutrient dense (Agenäs et al., 2003; Mashek & Beede, 2000; Rabelo et al., 2003; Vandehaar et al., 1999). These high-energy diets lead to overeating, providing significant energy before rumen fill. Drackley et al. (2014) demonstrated that cows fed high-energy diets during the dry period had greater serum concentrations of β-hydroxybutyrate, a ketone related to ketosis.

Increasing forage and fibers in a ration leads to rumen fill and reduces DMI, including grain and concentrates. There is evidence that feeding animals concentrates during the dry period does little more than needlessly fatten a cow (Grummer, 2008), leading to over-conditioned animals. Feeding concentrates to dry cows in addition to silage exacerbates the negative energy balance after calving and elevates serum concentrates of NEFA (Little et al., 2016), both of which correlate with incidence of postpartum ketosis. A survey of organic and conventional farms in the United States showed that ketosis is less common on farms where animals graze (Richert et al., 2013) and therefore achieve rumen fill through forage, lowering total DMI in a ration. Drackley and Cardoso (2014) emphasized the need to formulate feed rations for dry cows to limit excess energy intake in the lead-up to calving. These new studies contradict the "steam-up" theory of dry cow nutrition from the mid- and early twentieth century, which recommended increased levels of grain in pre-transition cows (Boutflour, 1928; Grummer, 2008).

Finally, recent studies suggest that lower stocking densities, separate calving pens, and longer recovery time for transition cows lowers rates of postpartum ketosis (Campler et al., 2019; Kaufman et al., 2016). Providing transitioning cows with more space and longer recovery time allows animals to have longer lying periods, which increases rumination, promotes better feeding behavior, and reduces competition for feed (Kaufman et al., 2016). Improved DMI and feeding post parturition leads to a shorter period of negative energy balance and is associated with a lower incidence of ketosis (Campler et al., 2019). Campler et al. (2019) report that extended time in maternity pens reduces stress on animals following calving.

Dehydration/electrolyte imbalance:
Preventive measures that should be taken in order to avoid dehydration and electrolyte imbalance in livestock include:
-Proper nutrition and hydration of the animals, specifically the pregnant animals (particularly during the last third of gestation) and neonatal calves (Stoltenow and Vincent, 2003).
-Adequate environment for the mother and neonatal calves: avoiding overcrowding and contamination of the space, maintaining proper sanitation dryness and cleanliness of the environment avoiding exposure to cold temperatures, rainfall and other stressful conditions (Stoltenow and Vincent, 2003).
-Proper administration of colostrum with adequate content of immunoglobulin G (IgG) for the neonatal calves (<2 hours after birth); colostrum IgG concentration appears to be an important factor that affects whether calves receive sufficient immunity from colostrum (Meganck et al., 2014).

Report Authorship

The following individuals were involved in research, data collection, writing, editing, and/or final approval of this report:

- Aura del Angel A Larson, Technical Coordinator, OMRI
- Peter O. Bungum, Senior Technical Coordinator, OMRI

- Phoebe Judge, Technical Coordinator, OMRI
- Tina Jensen Augustine, Senior Bilingual Technical Coordinator, OMRI
- Amy Bradsher, Deputy Director, OMRI
- Doug Currier, Technical Director, OMRI
- Peggy Miars, Executive Director/CEO, OMRI

All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11—Preventing Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.

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