Propylene Glycol
Livestock

Identification of Petitioned Substance

Chemical Names:
1,2-propanediol
Propane-1,2-diol
1,2-Propylene glycol
1,2-dihydroxypropane
2-Hydroxypropanol

Other Name:
Propylene glycol
Methylethyl glycol
Methylethylene glycol
Isopropylene glycol
Monopropylene glycol

Trade Names:
Keto Plus Gel;
Dairy & Beef Nutri-Drench;
Propylene Glycol USP 99.9%;
Propylene Advantage Energy Supplement

CAS Numbers:
57-55-6

Other Codes:
EPA Pesticide Chemical Code: 068603
EINECS: 200-338-0
InChi Key: DNIAPMSPPWPWGF-UHFFFAOYSA-N

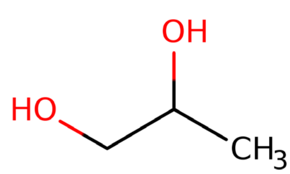
Summary of Petitioned Use

Propylene glycol is currently allowed for use under the National Organic Program (NOP) regulations at 7 CFR 205.603(a)(27) as a synthetic material only for the treatment of ketosis in ruminants. This report serves to provide technical information to complement the 2002 Technical Advisory Panel Report on propylene glycol for the National Organic Standards Board (NOSB)'s sunset review.

Characterization of Petitioned Substance

<u>**Composition of the Substance:**</u>
Propylene glycol, also called 1,2-propanediol, is a three-carbon diol (Sullivan, 1993). Its status as a diol (a molecule with two hydroxyl groups [-OH groups]) leads to its many uses as a polar material with a high boiling point (Sullivan, 1993; West et al., 2014). Propylene glycol is commercially available as a racemic mixture, meaning that it includes both the left- and right-handed versions of the molecule (isomers) (Sullivan, 1993; West et al., 2014). The two hydroxyls are located on carbons 1 and 2 (Fig. 1).

Figure 1. Chemical structure of propylene glycol (ChemIDplus, 2021)



<u>**Source or Origin of the Substance:**</u>
Propylene glycol is commercially produced through the hydrolysis of propylene oxide (Sullivan, 1993; Zhang et al., 2001). The original source of the propylene oxide is typically propylene, generated either through the steam cracking of hydrocarbons or through the dehydrogenation of propane, both of which are non-renewable sources (Barnicki, 2012; Saxena et al., 2010).

Researchers and manufacturers are improving methods to produce propylene glycol on a commercially viable scale via two additional routes:

- Catalytic hydrogenolysis of glycerol, a method that is becoming more economically feasible with the increased production of glycerol through biomass-produced ethanol (Berlowska et al., 2016; Chiu et al. 2008; Marchesan et al., 2019)
- Microbial fermentation through a number of different microorganisms (Marchesan et al., 2019; Veeravalli & Matthews, 2019)

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

Properties of the Substance:

Propylene glycol is a colorless, viscous liquid that is nearly odorless but faintly sweet in flavor. Table 1 summarizes the chemical and physical properties of propylene glycol.

Table 1. Chemical and Physical Properties of Propylene Glycol

Property	Description or Value
Physical state at 20 °C	Liquid
Color	Colorless
Odor	Nearly odorless
Molecular formula	$C_3H_8O_2$
Molecular weight (g/mol)	76.10
Density (g/cm^3) at 20 °C	1.0361
Dynamic viscosity (mPa · s) at 20 °C	56
Vapor pressure (kPa) at 20 °C	0.011
Melting point (°C)	-60
Boiling point (°C)	187.9
Specific heat capacity (kJ kg^{-1} K^{-1}) at 20 °C	2.49
Heat conductivity (Wm^{-1} K^{-1}) at 20 °C	0.20
Henry's Law Constant (atm · m^3/mol) at 25 °C	$1.3 \cdot 10^{-8}$
Log K_{ow}	-1.07
Log K_{oc}	-0.49

Data source: Sullivan (1993); US PubChem (2020); West et al. (2014)

Specific Uses of the Substance:

Propylene glycol has a wide range of uses, including as a chemical precursor to industrial production, as an ingredient in cosmetics, and as a disinfectant (Sullivan, 1993; West et al., 2014). This technical report focuses on its use in livestock health care for the treatment of ketosis in ruminants. This section also contains a brief description of the use of propylene glycol as an excipient ingredient in livestock health care inputs as well as uses beyond livestock care.

Ketosis

The allowed use of propylene glycol in organic production is only as a treatment for ketosis in ruminants (21 CFR 205.603(a)(27)). Propylene glycol is typically administered in an oral drench to animals showing signs of clinical ketosis or to animals that a producer suspects of having subclinical ketosis. Clinical ketosis includes symptoms such as loss of appetite, loss of body condition, a decrease in milk production, and increased levels of ketone bodies in blood (Baird, 1982; Nielsen & Ingvartsen, 2004). Subclinical ketosis exhibits through an excess of ketone bodies in an animal's blood, urine, and milk without the other observable signs of clinical ketosis (Duffield, 2000; McArt et al., 2012; Nielsen & Ingvartsen, 2004). Testing is often required to confirm subclinical ketosis. Both clinical and subclinical ketosis are also characterized by decreased level of blood glucose and increased levels of non-esterified fatty acids (NEFA) (Herdt, 2000; Nielsen & Ingvartsen, 2004).

Ketosis is a metabolic disease that can result from energy imbalance in early lactation. The majority of a dose of propylene glycol is not fermented in the rumen. Instead, it is directly absorbed and metabolized by the liver to form glucose (Emery et al., 1967; Grummer et al., 1994; Nielsen & Ingvartsen, 2004). The glucose aids when liver function is impaired soon after parturition (labor and delivery) (Grummer et al., 1994; Johnson, 1954; McArt et al., 2012). The metabolized glucose also serves as an energy supplement when nutritional demand outstrips dry matter intake later in the lactation period (Herdt, 2000). The proper dose of propylene glycol can aid in the recovery from both clinical and subclinical ketosis by stabilizing an animal's blood glucose level (Johnson, 1954; Grummer et al., 1994; Herdt, 2000; McArt et al., 2012).

Other Uses

Propylene glycol is generally recognized as safe (GRAS) by the U.S. FDA (21 CFR 184.1666) and is a common ingredient in several topical health care materials as an excipient ingredient. Propylene glycol is also a common ingredient in products such as lotions, balms, and salves due to its ability to retain moisture (e.g., Udder Comfort™; UltraCruz® Udder Balm®; KenAg Udder Cream).

Beyond livestock health care uses, propylene glycol is widely used in a number of manufacturing and food production roles. In food processing, propylene glycol serves as a humectant and a preservative (Barnicki, 2012; Hasenhuettl & Hartel, 2019). Propylene glycol is also used as a carrier in e-cigarette liquids (Scheffler et al., 2015) and is a common polyester resin in the manufacturing of automotive plastics and fiberglass as well as construction materials. Due to its low toxicity (especially relative to ethylene glycol) and high biodegradability, propylene glycol is commonly used as an aircraft deicer and as an automotive antifreeze solution (Bielefeldt et al., 2002; Klecka et al., 1993; Sullivan, 1993).

Approved Legal Uses of the Substance:

Food and Drug Administration (FDA)

Under FDA regulations, propylene glycol is allowed in animal drugs, feeds, and related products, with the exception of cat food (21 CFR 582.1666). The FDA first approved propylene glycol as GRAS for a broad range of direct food additive uses in 1982 (FDA, 2020). Propylene glycol is allowed in food in a wide variety of functions, including as an anticaking agent, an emulsifier, a flavor agent, a humectant, and as a texturizer. The FDA has also approved propylene glycol as an indirect food additive at 21 CFR 175, including uses in resinous and polymeric coatings, components in paperboard, rubber articles intended for repeated uses, and textile fabrics.

Environmental Protection Agency (EPA)

Propylene glycol is used both as an active pesticidal ingredient and as an inert ingredient. Propylene glycol is included on the 2004 EPA List 4B as an inert of minimal concern (US EPA, 2004). Propylene glycol is also considered a "commodity inert" and is therefore approved for food and non-food pesticidal use as an inert (US EPA, 2021a; US EPA, 2021b). The EPA has approved several propylene glycol-based pesticide products. Ozium® Air Sanitizer contains propylene glycol as an active ingredient (US EPA 2017). The EPA has also approved several disinfectant products that are made with registered pesticides and used with propylene glycol (e.g., Virkon S [EPA Reg. No. 39967-137] mixed with propylene glycol [US EPA 2019b]) used in poultry premises. These pesticide-propylene glycol combination products are used in poultry premises and facilities, are approved by the EPA, and their use is overseen by USDA's Animal and Plant Health Inspection Service (APHIS) (US EPA 2019a; US EPA 2019b).

Action of the Substance:

In organic production, propylene glycol is approved only as a treatment for ketosis in ruminants at 7 CFR 205.603(a)(27). Ketosis in ruminants can arise as a result of metabolic imbalance in pregnant and lactating animals when the animal's body is unable to produce or maintain a sufficient quantity of blood sugar (Herdt, 2000; Johnson, 1954; McArt et al., 2012; Nielsen & Ingvartsen, 2004). Propylene glycol provides a readily usable source of energy, allowing an animal's metabolism to resume proper function (Herdt, 2000; Johnson, 1954; Maplesden, 1954; Nielsen & Ingvartsen, 2004; McArt et al., 2011).

Ketosis in Ruminants

There are two types of ketosis prevalent in ruminants—ketosis that occurs within the first 3-7 days of parturition, and ketosis that occurs 4-6 weeks later at peak milk production during lactation (Baird, 1982; Herdt, 2000). Generally, ketosis refers to a metabolic state where an animal relies on a process that breaks down lipids (fats and oils) for energy instead of sugar (glucose). As a byproduct of this process, excess ketones are produced (Emery et al., 1964; Herdt, 2000). Under some conditions (primarily during gestation and lactation), the bodies of ruminant animals may rely more on lipid metabolism due to an imbalance between feed intake and nutritional demands (Herdt, 2000). During these times, animals may have difficulty synthesizing enough glucose (in a process called gluconeogenesis) to rely on it as an energy source, and instead shift to alternative metabolic pathways, such as lipid metabolism (Herdt, 2000; McArt et al., 2012; Vanholder et al., 2015).

The regulation mechanisms involved in metabolism are highly complex, and not all tissues within the animal respond in the same way (Herdt, 2000; Herdt, 2019; McArt et al., 2012). For example, mammary and placenta tissue cannot make efficient use of fats for metabolism and require adequate glucose supplies (Herdt, 2000). Most of the time, animals are able to adapt to keep up with the metabolic demands of gestation and lactation. However, if these feedback systems become imbalanced, animals may struggle to simultaneously maintain blood glucose levels and properly utilize alternative energy sources (such as fats) (Gordon et al., 2013; Herdt, 2000; Nielsen & Ingvartsen, 2004).

For an animal to remain healthy, it must be able to adapt to the new lipid metabolic state by regulating blood glucose, non-esterified fatty acids (NEFA), and other metabolically important molecules (Herdt, 2000). When an animal must rely on lipid metabolism, NEFA concentrations in blood serum may rise dramatically and can disrupt glucose synthesis in the liver (Herdt, 2000; Herdt, 2019). The liver breaks down NEFA into smaller molecules (ketones), which cells can use instead of glucose in aerobic respiration. These molecules themselves are involved in feedback systems that control gluconeogenesis (Herdt, 2000). Beta-hydroxybutyrate (BHB) is the most prominent ketone in ruminants, and it can serve as an energy source for many types of tissues (Zarrin et al., 2017). Elevated NEFA and ketone concentrations in serum, as well as decreased glucose concentrations, are indicators of subclinical and clinical ketosis (Herdt, 2000; Herdt, 2019; McArt et al., 2012; Nielsen & Ingvartsen, 2004).

Dairy Cows

During the transition from late pregnancy through labor and early lactation, ruminants commonly experience negative energy balance due to a simultaneous increase in energy requirements and a reduction in appetite and feed intake (Nielsen & Ingvartsen, 2004; McArt et al., 2012; Studer et al., 1993). This reduction in feed means that all sources of nutrients are diminished, including glucose (Herdt, 2000). In response, the animal's metabolism shifts to rely on stored lipids. When a dry cow is over-conditioned (overweight), the excess fat can disrupt proper metabolic feedback systems (Goff & Horst, 1997; Herdt, 2000). Over-conditioned cows can develop fatty liver disease, which can lead to fatty liver-derived ketosis (Grummer, 1993; Herdt, 2000). In these cases, even though the animals have a ready supply of stored lipids to fuel metabolism, the mammary tissue is unable to efficiently use these lipids (Herdt, 2000). Obesity in dry cows can create insulin resistance and loss of control of other metabolically important molecules, such as NEFA (Drackley et al., 2014; Duffield, 2000; Herdt, 2000; Nielsen & Ingvartsen, 2004; Vanholder et al., 2015).

The increased demand for energy paired with decreased appetite and feed intake reduce the availability of glucose and can push a cow toward subclinical ketosis (Grummer, 1993; Herdt, 2000; McArt, 2012). This type of parturition ketosis is sometimes referred to as "type II ketosis" (Herdt, 2000; Herdt, 2019). If a cow is untreated and her condition worsens, she may move toward clinical ketosis, suffering from depression, reduced milk production, and reproductive stress (Dohoo & Martin, 1984; McArt et al., 2012; Nielsen & Ingvartsen, 2004). Ketosis that occurs following parturition is commonly viewed as a management concern because it is often the result of over-conditioning during the dry period (Gerloff, 2000; Goff & Horst, 1997; Herdt, 2000; McArt et al., 2012; Studer et al.,1993), but risks of ketosis are also correlated with increasing lactations (Baird, 1982; McArt et al., 2012; Nielsen & Ingvartsen, 2004).

Dairy cows can also suffer from ketosis later in their lactation period, about 4–6 weeks after calving (Herdt, 2000; Nielsen & Ingvartsen, 2004). This type of lactation ketosis is sometimes referred to as "type I ketosis" (Herdt, 2000; Herdt, 2019). The negative energy balance that occurs later in lactation during peak milk production can lead to lactation ketosis (Baird, 1982; Herdt, 2000; Herdt, 2019). Lactation ketosis is harder to manage through prevention because the cow is unable to eat enough food to meet the energetic demand her body requires to produce significant amounts of milk (Herdt, 2000).

For cows, ketosis results in a reduction in milk production, as much as 1 kg per animal per day (Dohoo & Martin, 1984). Clinical ketosis can cause immobility, sending the animal into a positive feedback cycle of reduced mobility leading to reduced feed intake, furthering the negative energy imbalance in the animal. Ketosis can also include "nervous" symptoms, where an animal behaves erratically and dangerously, and can eventually lead to culling of animals (Duffield, 2000; Nielsen & Ingvartsen, 2004).

Dairy Goats and Sheep
Sheep and goats, especially individuals carrying multiple fetuses, commonly experience pregnancy toxemia (Cal-Pereyra et al., 2015). Pregnancy toxemia is a form of ketosis that happens very late in pregnancy or at the beginning of the lactation period due to the mobilization of stored fats, as is the case with cows during parturition ketosis (Cal-Pereyra et al., 2016; Ferraro et al., 2016). In sheep and goats, propylene glycol also serves as a precursor for glucose production in the liver (Ferraro et al., 2016).

Combinations of the Substance:
Propylene glycol is commonly sold generically as "Propylene Glycol" when its intended use is as a treatment for ketosis in ruminants, and the ingredients panel lists "Propylene Glycol" as 100 percent. Many of the largest manufacturers of veterinary products market "Propylene Glycol" products for treatment of ketosis. These veterinary products are also sold as "U.S.P. Propylene Glycol," the United States Pharmacopeia (USP) standard, which is a higher-purity grade of propylene glycol (Sullivan, 1993).

Status

Historic Use:
Conventional dairy producers use propylene glycol to treat ketosis, both prophylactically and when symptoms arise postpartum. Johnson (1954) established this use in 1954 and researchers have further refined the ideal dosage for both prepartum delivery and postpartuition drenching (Christensen et al., 1997; Emery et al., 1964; Grummer et al., 1994; Johnson & Combs, 1991; Maplesden, 1954). Mid-twentieth century researchers tried new approaches to treat ketosis symptoms, including hormone therapy as well as other sources of energy like glycerol and glucose, but many producers were still unsure of the causes of ketosis (Johnson, 1954; Maplesden, 1954). Nielsen and Ingvartsen (2004) report incident rates of clinical (1.1–9.2 percent) and subclinical (12–34 percent) ketosis in conventional bovine dairy production, while the rates of ketosis are not well studied for sheep and goats (Kalyesubula et al., 2019). Propylene glycol is one of the most common treatment methods for both subclinical and clinical ketosis in cows, and is also commonly used in sheep (Duffield, 2000; Ferraro et al., 2016; Zhang et al., 2020).

Organic Foods Production Act, USDA Final Rule:
The NOSB recommended adding propylene glycol to the National List in 2002 as an allowed synthetic material to be used to treat ketosis symptoms in ruminant animals (USDA, 2002). The National Organic Program (NOP) final rule currently allows the use of propylene glycol as a medical treatment for ketosis in ruminants (7 CFR 205.603(a)(27)). As a medical treatment, Subpart C of 7 CFR 205 specifies that producers shall not administer any drug in the absence of illness (7 CFR 205.238(c)(2)), limiting the use of propylene glycol to after the onset of ketosis symptoms, both clinical and subclinical, in ruminants.

International:
A survey of international guidelines and regulations for organic production from various countries and ruling bodies indicates that propylene glycol is generally an allowed input as a medical material when other preventative and natural input options are insufficient to prevent illness.

Canadian General Standards Board Permitted Substances List, CAN/CGSB-32.311-2020
The Canadian General Standards Board includes propylene glycol on CAN/CGSB 32.311-2020 Table 5.3 (Health Care Products and Production Aids) with the annotation, "May only be used as an ingredient in foot baths."

Table 5.3 also includes a listing for "Formulants (inerts, excipients)," allowing propylene glycol as an excipient used along with a permitted active ingredient.

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" clauses that producers must first prevent disease through species selection and management approaches. If prevention practices are insufficient to keep an animal healthy, a producer may use allopathic veterinary drugs if other homeopathic or phytotherapeutic products are insufficient. Propylene glycol is not explicitly mentioned for livestock health care input materials, but it would fall into the category of "veterinary drug" as defined in 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 in organic livestock production. Article 24, paragraph 3 indicates that if preventive methods and phytotherapeutic and homeopathic products are not effective at combating illness, a producer may use chemically synthesized veterinary medical products. In this case, propylene glycol would be considered a "veterinary medicinal product" under the definition at Article 1(2) of Directive 2001/82/EC of the European Parliament and of the Council concerning the Community code relating to veterinary medicinal products. A 48-hour withdrawal period between the last administration and the production of organically produced milk or meat is noted.

Japan Agricultural Standard (JAS) for Organic Production
Article 4 of the Japanese Agricultural Standard for Organic Livestock, last revised in April 2018, 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 therapy purposes. A withdrawal period of 48 hours between last use and milking or slaughter is noted.

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. Propylene glycol, when used to address 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

<u>Evaluation Question #1: Indicate which category in OFPA that the substance falls under:</u> (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) When used to mitigate or treat ketosis, propylene glycol acts as an animal drug (livestock medicine).
(B) Propylene glycol is an inert ingredient included on the 2004 EPA List 4B.

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)).

Hydrolysis of Propylene Oxide
The most common method for producing commercially available propylene glycol is through the hydrolysis of propylene oxide with water (Meher et al., 2009; Sullivan, 1993; Szmant, 1989; Zhang et al., 2001). In this process, manufacturers combine propylene oxide and water at a molar ratio of 1:15 at elevated temperatures and pressures (Sullivan, 1993). This produces an exothermic reaction and yields a mixture of propylene glycol, dipropylene glycol, and tripropylene glycol at a ratio of approximately 100:10:1 (Sullivan, 1993).

The propylene oxide used to produce propylene glycol may come from one of two main sources. The first source is from the chlorohydrin process, which combines propylene and aqueous chlorine (Sullivan, 1993; Szmant, 1989; Zhang et al., 2001). A second source is from the hydroperoxide process, which converts ethylbenzene to ethylbenzene hydroperoxide and then reacts with propylene to form propylene oxide (Vaishali & Naren, 2016). The primary sources for the propylene used to make the propylene oxide are through the steam cracking of hydrocarbons during petroleum distillation and through the dehydrogenation of propane (Barnicki, 2012; Saxena et al., 2010). Both sources are non-renewable resources.

Catalytic Hydrogenolysis of Glycerol
Manufacturers also convert glycerol into propylene glycol using a variety of catalysts (Lahr & Shanks, 2003; Marchesan et al., 2019; Sui et al., 2014). In this process, glycerol is first dehydrated using catalysts to form acetol. The dehydration product is then hydrogenated to produce propylene glycol (Chiu et al., 2008; Huang et al., 2008; Lahr & Shanks, 2003; Lahr & Shanks, 2005). In addition to using a variety of catalysts, manufacturers can use a suite of different carbon sources for glycerol and different temperatures to produce propylene glycol through the catalytic method (Dasari et al., 2005; Liu & Ye 2015; Meher et al., 2009; Pang et al., 2011; Zhang et al., 2001; Zhou et al., 2012).

Significant increases in global biomass-based diesel production have led to an increase in the supply of glycerol, which is a waste material generated during production of biodiesel (Liu & Ye, 2015; Marchesan et al, 2019; Pyne et al., 2016). Biomass-based diesel production increased almost 850 percent from 2005 to 2015 (US EIA 2020), yielding a source of waste that could be converted into industrial-grade propylene glycol (Jimenez et al., 2020). This production method is a current area of growth but is not commercially widespread (Jimenez et al., 2020).

Fermentation
There are a number of methods identified to produce propylene glycol via fermentation (Marchesan et al., 2019; Pagliaro et al., 2007; Zeng & Sabra, 2011). Recent work involves investigation of different carbon feedstocks, including:

- gluconate, glucose, sorbitol, and lactose (Altaras et al., 2001; Berríos-Rivera et al., 2003)
- glycerol derived from biomass-derived diesel (Joon-Young et al., 2011; Pyne et al., 2016)
- beet pulp (Berlowska et al., 2016)
- whey lactose (Veeravalli & Matthews 2019)

There are also several types of bacteria capable of producing propylene glycol, such as:

- *Thermoanaerobacterium thermossaccharolyticum* (Altaras et al., 2001)
- *Clostridium pasteurianum* (Pyne et al., 2016)
- *E. coli* (Bennett & San, 2001)

- *Lactobacillus buchneri* (Veeravalli & Matthews 2019)

Many of the available fermentation methods rely on genetically modified microorganisms for the efficient production of propylene glycol (Bennett & San, 2001; Berríos-Rivera et al., 2002; Joon-Young et al., 2011; Pyne et al., 2016). While these methods offer the potential to produce propylene glycol without relying on petrochemical byproducts, they are not economically competitive or available at commercial scale at this time (Marchesan et al., 2019; Veeravalli & Matthews, 2019).

<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)).

Hydrolysis of Propylene Oxide
There are three synthetic chemical steps commonly used to manufacture propylene glycol from the hydrolysis of propylene oxide. The first step is the production of the propylene, either through the steam cracking of hydrocarbons or through the dehydrogenation of propane (Barnicki, 2012; Saxena et al., 2010). The steam cracking method relies on heating hydrocarbons, often liquefied natural gas or naphtha, to very high temperatures in tubular reactors to separate the hydrocarbons into component molecules, including propylene (Amghizar et al., 2017). The dehydrogenation of propane relies on heating propane to approximately 650°C in the presence of platinum or other metal catalysts (Sui et al., 2014). The dehydrogenation process is strongly endothermic and removes an H_2 from the propane (C_3H_8) to form propylene (C_3H_6). Both propylene production methods rely on a chemical change due to heating of a non-biological matter which yields a synthetic material. See box 3 in NOP 5033-1 "Guidance: Decision Tree for Classification for Materials as Synthetic or Nonsynthetic."

The second step in this method is to convert propylene into propylene oxide via the chlorhydrin process or through the hydroperoxide process. Both of these common methods to produce propylene glycol transform the substance into a new, distinct substance using synthetic means. In the third and final step, manufacturers convert propylene oxide into propylene glycol by hydrolysis (described above in *Evaluation Question #2*).

Catalytic Hydrogenolysis of Glycerol
According to NOP 5033-1, synthetic/nonsynthetic classification starts with identifying the source of a substance, which in turn impacts how Box 1 is answered. Glycerol produced as a byproduct of biomass-based diesel production—a synthetic process (US DOE, 2020)—is not a natural source. Some of the glycerol feedstocks used in the hydrogenolysis process may be nonsynthetic, notably cellulose-derived glycerol from corn stalks or other cellulose-rich materials, but many of the treatments used to access the cellulose or carbohydrates involve synthetic steps such as applications of butanediol or hydrogen peroxide (Pang et al., 2011; Zhou et al., 2012).

Fermentation
As described in *Evaluation Question #2*, fermentation is not currently used in commercial production of propylene glycol. Some of the fermentation routes available to produce propylene glycol may represent potentially nonsynthetic, naturally occurring processes.

<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)).

Air
Propylene glycol does not absorb UV light above 300 nm, and there is little effect from photolysis by sunlight that contributes to its degradation in the atmosphere (West et al., 2014). The most direct method of degradation of propylene glycol vapor in the air is through reaction with hydroxyl radicals (NIH PubChem, 2020). The half-life of propylene glycol as a vapor is approximately 32 hours (NIH PubChem, 2020). Propylene glycol is unlikely to volatilize and enter the air column due to its low vapor pressure and high boiling point (West et al., 2014).

Water

Propylene glycol is resistant to hydrolysis between pH 4–9 at 25°C (West et al., 2014). Therefore, hydrolysis in many aqueous environments is unlikely to be a degradation mechanism for propylene glycol. Volatilization rates from water surfaces is low due to its low Henry's Law constant value (Table 1). With a very low K_{oc} value (-0.49), propylene glycol does not readily adsorb to suspended soil particles or sediments. However, West et al. (2007) demonstrated that propylene glycol is readily biodegradable in aqueous environments and shows significant biodegradability in seawater. While propylene glycol is unlikely to leave an aqueous environment through physical means (e.g., evaporation, adsorption) or degrade through hydrolysis, it is likely to biodegrade quickly.

Soil

Propylene glycol is highly mobile in soils; soil particles therefore do not slow down propylene glycol as it moves into groundwater (West et al., 2014).

In experiments where propylene glycol was applied directly to soil to model its use as an aircraft deicing fluid, it took 12 days for the propylene glycol to biodegrade completely when applied at rates of 0.05 percent (volume of fluid to weight of soil) (Klecka et al., 1993). However, Klecka and others (1993) also found that it took 111 days to degrade 76 percent when applied at a rate of 0.5 percent (volume of fluid to weight of soil). Additionally, when propylene glycol is mixed with other glycols (such as ethylene glycol or diethylene glycol), biodegradation is slower (Klecka et al., 1993; Pillard, 1995). In water-saturated sand columns designed to model catchment areas around airports, significant loading of propylene glycol in the sand decreases hydraulic conductivity, which is a measure of soil permeability (Bielefeldt et al., 2002). However, biodegradation of the propylene glycol, as well as time elapsed without the application of propylene glycol, results in the recovery of the original conductivity (Bielefeldt et al., 2002).

Toscano et al. (2013) showed that propylene glycol-degrading bacterial populations include *Pseudomonas* species, which are capable of utilizing propylene glycol as their sole source of carbon and energy. Jaesche et al. (2006) found that soil microorganisms are only able to degrade propylene glycol under warm weather conditions (20°C) but had little impact on the propylene glycol concentrations at colder temperatures (4°C). Additionally, soil biota degraded the propylene glycol significantly less under more "subsoil like" conditions, including lower porosity and higher bulk density conditions (Jaesche et al., 2006).

Evaluation Question #5: 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)).

Toxicity in Mammals

Propylene glycol is used in a wide variety of food and other consumer products, and the material has been the subject of significant acute and chronic exposure testing. In mammals, propylene glycol is not acutely toxic (NIH PubChem, 2020). The LD_{50} (dose at which 50 percent of the test animals die from exposure) for propylene glycol administered orally is relatively high: 8,000–46,000 mg/kg/day for rodents, and 18,000–20,000 mg/kg/day for rabbits and guinea pigs (US EPA, 2008). Clinical signs of distress from oral toxicity studies suggest that small mammals only experience distress from consuming propylene glycol when the doses approach lethal rates (US EPA, 2008). Dermal exposure to propylene glycol, including topical application and direct application to the eye, is tolerated well in test animals, though there appears to be some stinging or irritation when applied to mucous membranes (Rossoff, 1974). When inhaled, propylene glycol appears to have minimal impact beyond degradation of the tracheal lining in rabbits (US EPA, 2008).

Studies of subchronic exposure in dairy cows show no long-term effects when cows are given the standard dose of 500 mL daily for 35 days (Miyoshi et al. 2001). Treated cows had a shorter time to their first ovulation after calving and had a longer luteal phase (the period of time between ovulation and the end of the reproductive cycle) than the control populations (Miyoshi et al., 2001). Rizos et al. (2008) showed that there was no long-term impact to the reproductive system of the treated cows who received 500 mL of propylene glycol daily for many months. There appeared to be no change in reproductive qualities, including the follicular dynamics or in the oocyte quality for the treated animals, nor in the body condition or milk quality (Rizos et al., 2008).

Cats are the notable exception to the nontoxic impact of propylene glycol among mammals. When fed to cats at both low and high dose levels, propylene glycol drives the formation of Heinz bodies within red blood cells, which is associated with anemia (NIH PubChem, 2020). Propylene glycol also produces anion gap acidosis in the plasma of test animals, which can lead to renal failure (NIH PubChem, 2020). For this reason, the FDA specified that propylene glycol in or on cat food is not generally recognized as safe at 21 CFR 500.50.

There is little evidence of significant impact from propylene glycol on the reproductive health in test subjects including mice, rats, hamsters, rabbits, and guinea pigs (US EPA, 2008). When propylene glycol was injected into the yolk sac of chick embryos, there were no observed developmental impacts (NIH PubChem, 2020). However, when injected into the air sac, propylene glycol causes a high rate of mortality of chick embryos and has deleterious effect on about 20 percent of the surviving embryos (NIH PubChem, 2020). Otherwise, chronic exposure to sub-lethal doses of propylene glycol does not appear to cause reproductive or developmental abnormalities in test animals (NIH PubChem, 2020).

Propylene glycol shows some propensity toward mutagenicity. When a hamster fibroblast cell line was exposed to propylene glycol, researchers noted elevated instances of structural chromosomal aberrations, including chromosome gaps and fragmentations (NIH PubChem, 2020).

Toxicity in Avian Species

Due to the low volatility and the low toxicity of propylene glycol, the EPA does not expect there to be any effect to avian species because it does not reside in the air column for significant lengths of time (US EPA, 2006).

Toxicity in Aquatic Species

Propylene glycol does not readily move out of the water column. West, et al. (2014) compiled an extensive list of aquatic species and the LC_{50} (median lethal concentration in the environment) for propylene glycol associated with each species. Most aquatic vertebrate species have very high LC_{50} levels, with more than half above 40,000 mg/L. Clawed frog species were more susceptible to the impacts of propylene glycol with an LC_{50} value above 18,000 mg/L. The LC_{50} values for aquatic invertebrates were all above 10,000 mg/L (West et al., 2014). These values indicate that propylene glycol has a very low level of toxicity to aquatic vertebrates and invertebrates (West et al., 2014).

The primary degradation mechanism for propylene glycol is biodegradation, and its most significant by-product of consumption is CO_2 (West et al., 2014).

<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)).

Propylene glycol is widely used throughout many U.S. and global economic sectors. In 2006, the production capacity for propylene glycol in the United States was approximately 700 million liters (ICIS, 2007), and the majority of this capacity is through propane as part of the petrochemical reduction process. Production of propane can lead to significant environmental impacts, including greenhouse gas emissions, pollution of waterways, water use issues, and petrochemical spills (Ite & Ibok, 2013; Rivard et al., 2014; Vengosh et al., 2014). The manufacture of propylene glycol, when produced using propylene oxide via the chlorhydrin process (see *Evaluation Question #2* above), has environmental liabilities and generates dilute calcium chloride brine waste (Nexant, 2009).

The common usage of propylene glycol on dairy farms is in the prevention of ketosis where it is delivered in orally administered doses of 250–500 mL at a time. It is commonly sold in gallon-sized bottles for on-farm use (e.g., propylene glycol sold on the Valley Vet website [2020]), although it is also available in volumes up to 189 liters (50 gallons). In the treatment of ketosis, propylene glycol is used in small volumes and is virtually non-toxic to vertebrates and invertebrates (with the exception of cats). Its use on organic dairy farms presents a very low risk for environmental contamination. Beyond mishandling or leakage from packages, less than 1 percent of the propylene glycol used in a dose is excreted in milk, manure, or urine when used to treat ketosis (Emery et al., 1964). Contamination resulting from on-farm use is likely to be minimal.

Beyond usage on dairy farms, propylene glycol is commonly used as an aircraft deicing fluid because it is less toxic than ethylene glycol (Marin et al., 2010; Pillard, 1995). However, propylene glycol is significantly more toxic when used in combination either with ethylene glycol or with anti-corrosion or surfactant materials than when used alone (Cornell et al., 2000; Pillard, 1995). When used in aircraft deicing fluids, propylene glycol typically can biodegrade during the summer months when the fluids are not in use (Bielefeldt et al., 2002); there are experimental methods to treat the deicing fluids to prevent this degradation (Bausmith & Neufield, 1999; Marin et al., 2010). While direct application to fields is prohibited, there may be some minor application to fields through manure containing excreted propylene glycol from treated animals. Additionally, propylene glycol can accumulate under colder conditions or deeper into the substrate, reducing hydraulic conductivity and biodegradability (Bielefeldt et al., 2002; Klecka et al., 1993).

Evaluation Question #7: 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)).

Propylene glycol is used as a single-ingredient medical treatment for ketosis and is sold as USP-grade of at least 99.5 percent purity (Sullivan, 1993). It is not intended to be used in conjunction with other input materials, synthetic or nonsynthetic, when its purpose is to treat ketosis. Piantoni and Allen (2015) concluded that propylene glycol is more effective at raising plasma glucose levels and reducing ketosis symptoms when used alone than when used in combination with glycerol.

Under typical dairy farm condition, propylene glycol is used alone, stored in closed containers, and unlikely to chemically interact with other allowed synthetic or nonsynthetic materials. However, propylene glycol will ignite at 700 °F (371 °C) (HSDB, 2020). Propylene glycol is hygroscopic and must be stored in a closed container, and it will react with strong oxidizing agents, such as potassium permanganate (Rowe et al., 2009). Its breakdown products are carbon dioxide and water (O'Neil, 2006).

Oral drenching of dairy ruminants with propylene glycol is likely to lead to several types of human exposure. One type of common exposure is dermal contact during drenching of animals with propylene glycol. Several experiments show no irritation or sensitizing when applied to human skin, but exposure may heighten dermatitis symptoms (NIH PubChem, 2020). When propylene glycol comes into contact with eyes, it may cause immediate and temporary stinging, but it not likely to cause residual pain or injury (Grant, 1986). Inhalation of propylene glycol in the vapor form, a second potential method of exposure, may cause acute airway irritation (Wieslander et al., 2001). Propylene glycol is unlikely to cause long-lasting and serious damage to producers when used according to 7 CFR 205.603(a)(27).

Propylene glycol has been linked to toxicity in humans when used as a drug solubilizer, and it is related to the creation of serum creatinine when used in the delivery of lorazepam (Yaucher et al., 2003). Aye et al. (2010) report on *in vitro* DNA damage leading to chromosome mutations during the vitrification phase of oocyte preservation during assisted reproduction techniques. Propylene glycol is commonly used in vape pods for electronic cigarettes and in theatrical productions as fog, both uses of which are likely to produce respiratory irritation (NIH PubChem, 2020). However, none of these uses is consistent with the inclusion of propylene glycol on the National List.

Evaluation Question #8: 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)).

The use of propylene glycol in ruminant livestock to treat ketosis after symptoms appear is not linked to long-term physiological changes in behavior, fertility, metabolism, or other parameters (see *Evaluation Questions #5* and *#6)*. While drenching of animals with propylene glycol reduces ketosis symptoms in ruminants, its use does not appear to reduce the recurrence of ketosis in subsequent lactations (Nielsen & Ingvartsen, 2004).

Ketosis is a metabolic disease that has significant consequences on energy use and intake (Gordon et al., 2017; Herdt, 2000; Johnson, 1954; Nielsen & Ingvartsen, 2004). Animals experiencing metabolic imbalance may suffer from depressed milk production, reduced fertility, and increased occurrence of displaced abomasum (Dohoo & Martin, 1984; McArt et al., 2012; Nielson & Ingvartsen, 2004). Producers give their animals propylene glycol to improve the metabolic imbalance; therefore, the use of propylene glycol does have positive short-term effects. The use of propylene glycol to treat ketosis also increases milk production in animals with subclinical and clinical ketosis (Dohoo & Martin, 1984; Gordon et al., 2017; Juchem et al., 2004; Lomander et al., 2012; Nielsen & Ingvarten 2004). In a study conducted by McArt et al. (2011), animals experiencing ketosis that were treated with propylene glycol increased their milk production 10–13 percent over those not treated. However, other investigators found no significant increase in milk production (Chung et al., 2009; Juchem et al. 2004; Pickett et al., 2003; Studer et al., 1993). McArt et al. (2011) theorized that research demonstrating the lack of increased milk production in treated animals may be related to overall prevalence of ketosis across a herd or the size of the herds in each study. When few cows in a herd experience ketosis in a trial period, or when the herd size is small, McArt et al. (2011) suggested that the increases in milk production may not be statistically significant.

Propylene glycol impacts the fertility of treated animals. Hackbart et al. (2017) found a reduction in the fertilization rates of egg cells in cows treated with propylene glycol, but noted that when fertilization occurred, embryos developed normally in treated animals. Propylene glycol also appears to lengthen the luteal phase in treated animals when compared to untreated animals (Nielsen & Ingvartsen, 2004).

For the treatment of ketosis, propylene glycol is not applied to the soil and is unlikely to interact with the agro-ecosystem outside of the treated animal. Propylene glycol is not likely to be unintentionally applied to soil through manure. Emery et al. (1964) reported that the body retention rate in cows, even when fed 5.4 pounds per day of propylene glycol, is over 99 percent, and that the excretion in milk is below the detection limit (0.1 percent).

<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)).

Based on currently available information, propylene glycol is:

- not acutely toxic and it has a high lethal concentration in both mammals and aquatic species
- readily decomposed into carbon dioxide and water by microorganisms in water and soil, and breaks down in air through reaction with hydroxyl radicals
- able to move rapidly through the environment with water, and shows little to no bioaccumulation
- efficiently retained and consumed as energy for animals so that it will not be applied to soils through manure incorporation

At doses above 500 mL per day for cows and 250 ml for ovine and caprine species, propylene glycol does not have a lasting physiological impact on the animals, and it provides readily available necessary energy for animals who are experiencing ketosis symptoms. There are adverse impacts when propylene glycol is used at rates that exceed the recommended dosages, including animals experiencing depression (Nielsen & Ingvartsen, 2004; Zhang et al., 2020).

A model of propylene glycol use on a medium-sized (~200 cows) dairy farm would begin with the approximation that each dairy cow calves once per year. The rate of ketosis on dairy farms may be as high as 20–30 percent (Nielsen & Ingvartsen, 2004; Richert et al., 2013). Assuming a rate of 25 percent ketosis incidence, a 200-cow dairy farm would have 50 cows per year receive propylene glycol. Based on label directions, a typical use rate is 475 mL per cow per day for four days after the onset of ketosis symptoms (e.g. AgriLabs Propylene Glycol label instruction), although dosage and treatment lengths vary. At this rate, cows on the farm would consume 95 L of propylene glycol per year, roughly 25 gallons. Assuming that, at maximum, approximately 1 percent of the material is excreted from cows via urine and manure (Emery et al., 1964), this would result in a total of about 1 L of propylene glycol entering the waste stream on the farm. Based on the data presented in *Evaluation Questions 2–8,* and the intended use, it is unlikely that the use of propylene glycol is harmful to the environment.

<u>Evaluation Question #10:</u> 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)).

Based on the data and information presented in *Evaluation Questions 2-8*, the majority of the impacts from propylene glycol on human health are restricted to dermal and inhalation risks when applying it as a treatment for ketosis. Producers are likely to be exposed to propylene glycol when orally drenching animals (NIH PubChem, 2020). When inhaled, propylene glycol may cause acute respiratory irritation (Wieslander et al., 2001). Neither of these impacts should not have serious or long-lasting impacts on skin or airways given the low toxicity and short exposure times.

<u>Evaluation Question #11:</u> 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)).

Molasses

Molasses, when added 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). Havekes et al. (2020) report that cows fed 1 kg of molasses per day during the dry period showed a higher feeding rate and dry matter intake immediately prior to calving and a decrease in BHB levels post-parturition. Increasing feed immediately before and following labor and delivery allows animals to reduce the length of negative energy balance and to stabilize their metabolism (Herdt, 2000; McArt et al., 2012; Vickers et al., 2013). These clinical research findings are consistent with working knowledge gained from farmer experimentation (Jodarski, 2020; Lans et al., 2007). There are fewer studies on ovine species and their response to ketosis treatment materials as compared to studies of dairy cows. Sheep do not appear to respond as successfully to molasses as cows (Ferraro et al., 2016).

Because molasses used to treat ketosis symptoms is a health care use, producers would be able to use non-organic molasses. When fed routinely for several months, certification agencies are likely to require organic molasses as part of a feed ration. Both materials are readily available, and a search of the Organic Integrity Database shows 164 producers of organic molasses as of February 26, 2021.

Glycerin

Glycerin, or glycerol, can be made synthetically or nonsynthetically. Synthetic sources are allowed at 7 CFR 205.603(a)(14) for inclusion in teat dips but not for the treatment of ketosis. However, nonsynthetic sources could be used for the treatment of ketosis since these nonsynthetic glycerin sources derived from steam hydrolysis of agricultural materials or fermentation are not prohibited for use in livestock production. Glycerin has a slightly sweet taste, and it acts to increase the palatability of feed rations. It can be delivered either as an oral drench or combined in the feed ration.

Numerous studies have illustrated the benefits of using glycerin to treat ketosis in sheep over other materials (Cal-Pereyra et al., 2015; Ferraro et al., 2016; Kalyesubula et al., 2019). Sheep respond well to either glycerin alone (Kalyesubula et al., 2019) or to a combination of glycerin and propylene glycol (Cal-Pereyra et al., 2015). Glycerin reduces the ketone BHB in blood for longer and elevates blood glucose more than propylene glycol in sheep (Kalyesubula et al., 2019).

In a meta-analysis of research studies, cows were shown to also respond well to glycerin, and glycerin can be used at much higher rates than propylene glycol (Kupczynski et al., 2020). However, glycerin is about half as effective as propylene glycol in cows (Piantoni & Allen, 2015), requiring twice as large of a dose to achieve similar results to propylene glycol. Glycerin is efficiently metabolized in both the rumen and in the liver, and may function well to treat ketosis (Kupczynski et al., 2020). However, at high dosages, there may be negative impacts on biodiversity in the rumen, and work remains to clarify rumen impact of glycerin use (Kupczynski et al., 2020).

Glucose

Glucose (sometimes referred to as dextrose) is a commonly used remedy to ketosis in ruminants and might be found in nonsynthetic forms. It is commonly sold in a 50 percent solution with water and is administered intravenously at a rate of 50 cc per 100 lbs body weight of the animal. When delivered intravenously, glucose provides an immediate delivery of sugars to the blood stream and effectively treats nervous ketosis, 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 et al., 2010). Glucose provides less than 12 hours of suppression of BHB, 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 et al., 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).

Choline and B Vitamins

Choline and other B vitamin complexes are also possible treatments for ketosis. However, these materials may only be commercially available in synthetic forms. Synthetic vitamins are allowed at 7 CFR 205.603(a)(21) as injectable nutritive supplements. Pinotti et al. (2002) found choline to be a limiting nutrient for milk production in cows, especially in high-yielding animals. Research suggests that choline may increase the dry matter intake of cows, which would help counteract decreased intake commonly observed in early lactation, but may also increase milk production, which would neutralize any impact on the energy balance (Humer et al., 2019). Choline may also act to enhance the export of very low-density lipoproteins from the liver of dairy animals, and the removal of these lipoproteins from the liver helps to prevent fatty liver disease (Grummer, 2008). Fatty liver disease is the form of early-lactation ketosis that affects over-conditioned animals, and the increased choline can help to reduce the incidence of fatty liver. In a meta-analysis of a number of studies involving the increased delivery of choline to cows, Humer et al. (2019) highlighted the variability in results. Some studies showed a lower incidence of ketosis in dairy cows treated with choline, while other studies did not show a decrease.

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

Subclinical and clinical ketosis can result in significant milk loss and other serious health impacts, including death. As a result, many producers strive to respond to symptoms of ketosis as quickly as possible to prevent the loss of milk and possibly of the animal.

One of the major risk factors for parturition ketosis is if animals are over-conditioned or have elevated adipose tissue when entering the dry period (Drackley et al., 2014; Duffield, 2000; Vanholder et al., 2015). Over-conditioned cows are more likely to suffer from fatty liver symptoms (see *Action of the Substance* section). Duffield (2000) reported that overweight cows are almost twice as likely to experience subclinical ketosis during lactation. Richert et al. (2013) also reported that feeding higher level of concentrates (i.e., feeds that are high in protein or energy but relatively low in fiber) or grains correlated with higher occurrence of ketosis in organic herds. Additionally, increased rates of hyperketonemia are correlated with excess feeding during the entire dry period (Mann et al., 2015; Vickers et al., 2013).

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 as conventional animals (Hardeng et al., 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., 2014), 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 (Van Soest et al., 1991; Litherland et al., 2013). Lower levels of serum NEFA is negatively correlated with subclinical and clinical ketosis in cows (Drackley et al., 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 beta-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.

Report Authorship

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