United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/national-list/petitioned

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Atropine
Livestock

Identification of Petitioned Substance

Chemical Names:
Atropine
Atropine Sulfate
(+)-Hyoscyamine
(-)-Hyoscyamine
D-Hyosyamine
L-Hyosyamine
[(1R, 5S)-8-methyl-8-azabicyco[3.2.1]octan-3-yl]
3-hydroxy-2-phenylpropanotate

Other Names:
Tropine Tropate
Atropin
Atropen
(+-)-Atropine
Trolyl Tropate

Trade Names:
Atropine Care 1%
Atropisol®
Isopto® Atropine
Ocu-Tropine®
AtroJect SA™
Atropine Sulfate Injection

CAS Numbers:
51-55-8 (Atropine)
13269-35-7 (Atropine Sulfate)

Other Codes:
EC No. 200-104-8 (Atropine)
EC No. 202-933-0 (Atropine Sulfate)
UN No. 1544

Summary of Petitioned Use

Atropine is currently allowed by the United States Department of Agriculture (USDA) organic regulations as a medical treatment for organic livestock production (7 CFR 205.603(a)). USDA organic regulations restrict atropine to "use by or on the lawful written or oral order of a licensed veterinarian," and it must be followed by "a meat withdrawal period of at least 56 days after administering to livestock intended for slaughter; and a milk discard period of at least 12 days after administering to dairy animals." This technical report outlines the veterinary applications of atropine for organic livestock production and serves to update a previous technical report from 2002 (USDA 2002).

Characterization of Petitioned Substance

Composition of the Substance:
Atropine is a naturally occurring alkaloid (a nitrogen-containing molecule that is produced in plants and is physiologically active) produced by the plants in the nightshade family (EFSA 2008, Timberlake 2015). Atropine is primarily isolated from *Atropa belladonna* (also known as deadly nightshade) and is a component in both human and veterinary medicines for a range of treatments. Although, it is most widely used in both human and veterinary practices as a treatment for organophosphate poisoning (PubChem 174174, Rinaldi and Himwich 1954, Bunke et al. 1996, Reist et al. 1997, EMEA 1998, Karalliedde 1999, Chugh et al. 2005, Eddleston et al. 2005, Eddleston et al. 2006, Aardema et al. 2008, EFSA 2008). When used as an anticholergic drug for organophosphate treatment, atropine may be combined with oximes (primarily pralidoxime (PAM)) (Karalliedde 1999, WHO 1999, Kassa 2002). Oximes are a class of molecules that have been shown to reverse symptoms of phosphate poisoning through a mechanism complimentary to that of atropine (Shih 1993, Karalliedde 1999, WHO 1999, Kassa 2002). Pralidoxime is the most common oxime administered for organophosphate poisoning treatment (Singh et al. 1998, Kassa 2002, Chugh et al. 2005, Eddleston et al. 2005, Eddleston et al. 2008). It is a white substance that is typically administered as a halogen salt (Kassa 2002).

eSource or Origin of the Substance:

Atropine is a naturally occurring alkaloid (a nitrogen-containing molecule that is produced in plants and is physiologically active) produced by plants in the nightshade family (EFSA 2008, Timberlake 2015). The primary source of atropine is accessed by extraction from *Atropa belladonna*, which yields the racemic mixture of (+)-hyoscyamine and (-)-hyoscyamine (atropine) (Figure 1). Atropine may also be synthesized in an acid-catalyzed esterification reaction in between tropine and tropic acid, although the primary source of atropine is from plant extracts (PubChem 174174, Karkee 1980, Merck 2001, USDA 2002, EFSA 2008).

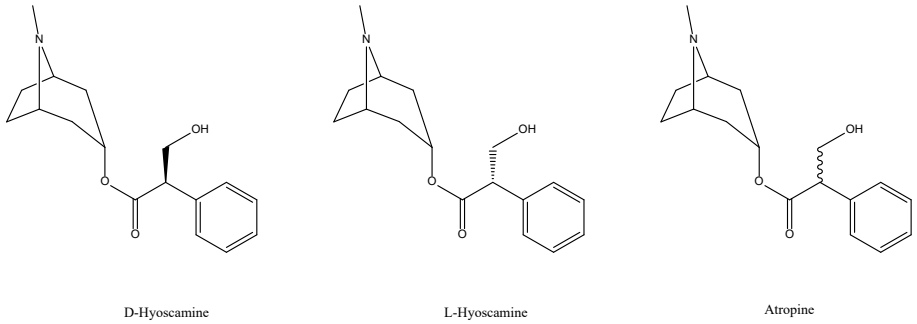


Figure 1

Properties of the Substance:

The properties of atropine are summarized below in Table 1.

Table 1. Properties of Atropine

Compound	Atropine
CAS No.	51-55-8
Molecular Weight	289.37 g/mol
General Appearance	White crystals or powder
Water Solubility	2200 mg/L (at 25 °C)
Melting Point	115 °C
pH	10.00 (0.0015 M)

Sources: Merck 2001, PubChem 174174, Sigma-Aldrich 2018a.

Specific Uses of the Substance:

Atropine is used in organic agricultural livestock production as a veterinary medicine for a variety of treatments and can be administered as a tablet, intravenously, injection, or can be absorbed through the skin (EMEA 1998, Karalliedde 1999, Eddleston et al. 2004, Eddleston et al. 2006).

Organophosphate Poisoning

Organophosphate poisoning is most commonly caused by the ingestion of pesticides that are common in some agricultural settings (Karalliedde 1999, Kassa 2002, Chugh 2005, Eddleston et al. 2005, Eddleston et al. 2006, Kumar et al. 2010). Atropine has long been acknowledged as the cornerstone of organophosphate treatment options for both human and veterinary cases due to its antimuscarinic (ability to block the effects of the neurotransmitter muscarine) properties (WHO 1999, Robenshtok et al. 2002, Eddleston et al. 2006, Flomenbaum et al. 2006, Eddleston et al. 2008, Kumar et al. 2010). While atropine relieves symptoms associated with organophosphate poisoning, it is not an antidote, as it does not reverse the biochemical effect of the organophosphate (USDA 2002). Atropine alleviates symptoms by competing with acetylcholine (a neurotransmitter) for receptor binding sites (Rinaldi and Himwich 1954, EMEA 1998, Karalliedde 1999, Merck 2001, Chugh et al. 2005, Eddleston et al. 2005, Eddleston et al. 2006, Flomenbaum et al. 2006, Aardema et al. 2008, Timberlake 2015).

Anesthesia Pretreatment

Atropine is also used in veterinary medicine as a pretreatment for anesthesia (EMEA 1998, USDA 2002). The same antimuscarinic properties that provide relief for organophosphate poisoning work to reduce secretions (e.g., sweat, saliva) and relax smooth muscles prior to the administration of anesthesia, reducing

the risk of airway obstruction (Jones et al. 1977, USDA 2002, Brunton et al. 2006, EFSA 2008). The application of atropine along with anesthesia also works to regulate heart rate (Ilkiw et al. 1993, EMEA 1998, Pimenta et al. 2011).

Bradycardia

Atropine also produces a neurological response that is useful for the treatment of bradycardia (low heart rate) (Ilkiw et al. 1993, Ellenhorn et al. 1997, EMEA 1998, Aardema et al. 2008, EFSA 2008, Pimenta et al. 2011). Atropine's antimuscarinic (ability to block the effects of the neurotransmitter muscarine) properties result in heart stimulation at the central vagus nerve, increasing heart rate in bradycardia cases (Williams et al. 2000 Flomenbaum et al 2006).

Ophthalmic Applications

Atropine has several ophthalmic (eye-care) applications due to its ability to induce pupil dilation and cycloplegic properties (paralysis of eye muscles) (EMEA 1998, Herring et al. 2000). As previously discussed, atropine's ability to act as a muscarinic antagonist relaxes smooth muscle tissue. When applied to the eye, these relaxations act to reduce pain and dilate pupils, making it useful for treatment in equine uveitis and as a presurgical treatment for cataract extractions (Herring et al. 2000, Williams et al. 2000, MedlinePlus 2017). The substance has also been shown to increase the membrane permeability within the iris, controlling protein migration and subsequent inflammation of the eye (Williams et al. 2000).

Approved Legal Uses of the Substance:

The USDA NOP allows atropine for veterinary applications within organic livestock production at 7 CFR 205.603 with the restriction to "use by or on the lawful written or oral order of a licensed veterinarian," and it must be followed by "a meat withdrawal period of at least 56 days after administering to livestock intended for slaughter; and a milk discard period of at least 12 days after administering to dairy animals."

The United States Food and Drug Administration (FDA) has approved atropine for a range of uses within human and veterinary medicine applications. Atropine is approved for use as an ingredient or cotreatment to several medicinal substances. The FDA has approved atropine for use with trichlorfon "for the treatment of *Syphacia obvelata* (pinworm) in laboratory mice," with the administration being limited to "1.67 grams of trichlorfon and 7.7 milligrams of atropine per liter continuously for 7 to 14 days as the sole source of drinking water" and with the limitation that the treatment is restricted "to use by or on the order of a licensed veterinarian" at 21 CFR 520.2520. The FDA has approved atropine for use as a pretreatment to pralidoxime for poisoning treatment at §522.1862 in which "atropine is administered intravenously at a dosage rate of 0.05 mg per pound of body weight, followed by administration of an additional 0.15 mg of atropine per pound of body weight administered intramuscularly." Atropine is allowed by the FDA as a component of "narcotic drugs containing non-narcotic active medicinal ingredients," at §1308.15, with the controlled restrictions of "not more than 2.5 milligrams of diphenoxylate and not less than 25 micrograms of atropine sulfate per dosage unit," and "not more than 0.5 milligrams of difenoxin and not less than 25 micrograms of atropine sulfate per dosage unit."

The FDA allows the use of atropine with droperdiol and fentanyl "for analgesia or tranquilization," at §522.800, with "atropine sulfate administered at the rate of 0.02 mg per pound of body weight." Atropine, and atropine mixtures, is typically administered via intravenous injection (EMEA 1998, Williams et al. 2000, Eddleston et al. 2004, Chugh 2005, Flomenbaum et al. 2006).

Atropine has been approved by the FDA as an "active ingredient offered over-the-counter (OTC) for human use as an anticholinergic [substances that shut down neurological signals from choline neurotransmitters through competition for receptors, breaking down choline, or preventing the release of choline] in cough-cold drug products" at 21 CFR 310.533 (Timberlake 2015). Atropine acts as an active ingredient in anticholinergic medications "to relieve excessive secretions of the nose and eyes, symptoms that are commonly associated with hay fever, allergy, rhinitis, and the common cold." at §500.55. The FDA has also approved atropine as an antidotal treatment for dichlorvos (an organophosphate widely used as an insecticide) poisoning at §558.205.

Action of the Substance:

Organophosphate Poisoning

Organophosphate poisoning is most commonly caused by the ingestion of pesticides (Karalliedde 1999, Kassa 2002, Chugh 2005, Eddleston et al. 2005, Eddleston et al. 2006, Kumar et al. 2010). However, organophosphates present in antiparasitic treatments (e.g., lice, ticks) are another source of livestock poisoning (Karalliedde 1999). Atropine is the primary means of treating organophosphate poisoning in both human and veterinary medicine (Kassa 2002, Robenshtok et al. 2002, Eddleston et al. 2006, Eddleston et al. 2008, Kumar et al. 2010). Organophosphates are widely used as insecticides in agricultural settings, but they are poisonous to both humans and livestock and cross respiratory membranes when inhaled, gastrointestinal membranes when ingested, and are readily absorbed through the skin (Karalliedde 1999, Kassa 2002, Eddleston et al. 2004, Eddleston et al. 2005, Eddleston et al. 2008, Kumar et al. 2010). Organophosphates irreversibly inhibit the enzyme acetylcholinesterase (an enzyme that turns off neurological signals caused by acetylcholine by breaking down the neurotransmitter) by bonding to the active site of the enzyme, and atropine works to reverse this effect by reversibly binding to acetylcholine receptors (Rinaldi and Himwich 1954, EMEA 1998, Eddleston et al. 2005, Eddleston et al. 2006, Aardema et al. 2008, Eddleston et al. 2008, EFSA 2008, Kumar et al. 2010, Haddad and Winchester 1983).

The competitive binding of atropine reduces the sites available for acetylcholine binding, and therefore, reduces the effects of acetylcholine overexpression (Rinaldi and Himwich 1954, Eddleston et al. 2004, Chugh et al. 2005, Eddleston et al. 2005, Eddleston et al. 2006, EFSA 2008). When atropine is introduced, the symptoms of organophosphate poisoning (miosis, blurred vision, nausea, salivation, bradycardia, bronchospasm, abdominal pain, incontinence, muscle weakness, hypertension, confusion, fatigue, unconsciousness, and respiratory depression) subside as the acetylcholine neurotransmitter diffuses from the synapse or is returned to the neuron for storage (Timberlake 2015, Eddleston et al. 2006, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). Moreover, the neurophysiological effects of atropine (e.g., smooth muscle relaxation, inhibited excretion, vagal nerve stimulation) result in the increased efficacy of subsequent treatments (e.g., oximes, oxygenation treatments) (Kassa 2002, Eddleston et al. 2004, Eddleston et al. 2006, Eddleston et al. 2008).

The combination of neurological competition with acetylcholine and stabilizing physiological effects have resulted in atropine treatment being widely recognized as the global cornerstone for organophosphate poisoning in both human and veterinary medicine (WHO 1999, Robenshtok et al. 2002, Eddleston et al. 2005, Eddleston et al. 2006, Eddleston et al. 2008, Kumar et al. 2010). However, because atropine works through competition with acetylcholine for neurological binding sites, there is no well-defined dosage for treatment. The required dosage is instead based upon both the species of animal being treated, as well as the quantity of poison that has been absorbed (Rinaldi and Himwich 1954, EMEA 1998, Eddleston et al. 2004, EFSA 2008).

Treatment protocols are centered around increasing the quantity of atropine administered until the symptoms of organophosphate poisoning begin to recede, or those of atropine poisoning begin to be expressed (Kassa 2002, Eddleston et al. 2004, Eddleston et al. 2008). Like organophosphates, atropine is readily absorbed and transported throughout the body, and can pass the blood-brain barrier (Eddleston et al. 2006). The rapid absorption of atropine results in facile physiological responses, an important factor in treatment choice, and allowing the monitoring of treatment protocol which helps over-administration of atropine in antidotal treatments (Rinaldi and Himwich 1954, Eddleston et al. 2004, Eddleston et al. 2006, Aardema et al. 2008, Eddleston et al. 2008).

Anesthesia Pretreatment

The mode of action of atropine as a pretreatment for anesthesia is like treating organophosphate poisoning. Atropine competes with acetylcholine, reducing the neurological choline response, and resulting in the relaxation of smooth muscles and inhibition of excretions (e.g., saliva, sweat) (Rinaldi and Himwich 1954, EFSA 2008). These responses increase the safety of anesthesia applications by increasing the flow of oxygen and reducing potential choking hazards (Ilkiw et al. 1993).

Bradycardia
The treatment of bradycardia (low heart rate) occurs through the ability of atropine to stimulate the central vagal nerve (Williams et al. 2000). This stimulation produces a parasympathetic physiological response that increases heart rate, an important factor in treatment of organophosphate poisoning and in applications following surgery as the patient returns from anesthesia (Ilkiw et al. 1993, Eddleston et al. 2006, Aardema et al. 2008, Eddleston et al. 2008, Pimenta et al. 2011).

Ophthalmic Applications
As in the previous applications, the mode of action for atropine is much the same. Competition with acetylcholine results in antimuscarinic physiological responses, including relaxing smooth (ocular) muscle tissue (Rinaldi and Himwich 1954, EMEA 1998, Herring et al. 2000, Williams et al. 2000). The resulting muscle relaxation decreases ocular pain, but also dilates the pupils, which is useful for surgical procedures such as cataract extraction (EMEA 1998, Williams et al. 2000, MedlinePlus 2017). Atropine has also been shown to be an effective means to increase permeability of the iris, making it a useful treatment option for inflammation and glaucoma (Williams et al. 2000).

Combinations of the Substance:
Atropine may be combined with many medicinal substances as a treatment or pretreatment, depending on the application. In livestock production, it is most commonly combined with oximes for organophosphate treatments (WHO 1999, Kassa 2002, Eddleston et al. 2004, Chugh et al. 2005, Eddleston et al. 2006). The most common oxime used with atropine is pralidoxime, which rather than competing with acetylcholine (like atropine), acts to restore the activity of the acetylcholinesterase by dephosphorylating the enzyme active site (Singh et al. 1998, Kassa 2002, Eddleston et al. 2004, Chugh et al. 2005, Eddleston et al. 2008).

USDA organic regulations permit the addition of some excipients to livestock drugs, defined at 7 CFR 205.2 as, "ingredients that are intentionally added to livestock medications but do not exert therapeutic or diagnostic effects at the intended dosage, although they may act to improve product delivery (e.g., enhancing absorption or controlling release of the drug substance)." Allowed excipients must be: identified by the FDA as Generally Recognized as Safe, approved by the FDA as a food additive, or included in the FDA review and approval of a New Animal Drug Application or New Drug Application (7 CFR 205.603(f)).

Status

Historic Use:
Atropine has seen extensive use in both human and veterinary medicinal applications dating back to the 1500s (EFSA 2008). The neurological activity of the substance has proved useful in medicinal applications from the treatment of symptoms of the common cold and neurotoxins, including organophosphates and mushroom toxins (Robenshtok et al. 2002, Eddleston et al. 2006, Eddleston et al. 2008, EFSA 2008, Kumar et al. 2010).

Within the context of livestock veterinary applications, atropine has been used in a variety of ways as have been described in detail in the Characterization of Petitioned Substance: a treatment for organophosphate poisoning by reversibly blocking acetylcholine receptors; a preanesthetic for veterinary surgical procedures due to its ability to reduce secretions and relax muscles; a bradycardia treatment to raise heart rates following anesthesia in surgical procedures; a veterinary ophthalmological treatment as it relaxes ocular muscles, relieves pain, dilates pupils, and affects iris permeability for glaucoma treatments (EMEA 1998, Herring et al. 2000, Williams et al. 2000, MedlinePlus 2017).

Organic Foods Production Act, USDA Final Rule:
Atropine is not specifically listed in the Organic Foods Production Act of 1990 (OFPA), although OFPA allows synthetic livestock medicines to be added to the National List (7 U.S.C. §6517(c)(1)). Atropine is allowed by current USDA organic regulations for livestock production, but is restricted to "use by or on the lawful written or oral order of a licensed veterinarian," and treatment must be followed by "a meat

withdrawal period of at least 56 days after administering to livestock intended for slaughter; and a milk discard period of at least 12 days after administering to dairy animals" at 7 CFR 205.603.

International

Canadian General Standards Board Permitted Substances List —
Atropine is listed in the CAN/CGSB-32.311-2015 — Organic production systems - permitted substances lists in Table 5.3 "health care products and production aids," as a "medicine from herbaceous plants," and must be "used according to label specifications."

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999) —
Atropine is not listed in the CODEX.

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008 —
Atropine is not listed in the EEC EC No. 834/2007 or 889/2008.

Japan Agricultural Standard (JAS) for Organic Production —
Atropine is not listed in the JAS for Organic Production.

International Federation of Organic Agriculture Movements (IFOAM) —
Atropine is not listed in IFOAM.

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) Atropine is the active ingredient in medicines for several veterinary applications and falls under the OFPA category of livestock medicine. The primary application is for treatment of organophosphate poisoning, in which the substance reversibly competes with the overexpressed neurotransmitter acetylcholine to alleviate the potentially fatal symptoms of organophosphate poisoning (Robenshtok et al. 2002, Eddleston et al. 2006, Eddleston et al. 2008, Kumar et al. 2010). Atropine is also used for the veterinary treatment of bradycardia and is used as a pretreatment for anesthesia and ophthalmic applications (e.g., cataract extractions, dilation of pupils) (Ilkiw et al. 1993, Ellenhorn et al. 1997, EMEA 1998, Herring et al. 2000, Williams et al. 2000, Aardema et al. 2008, EFSA 2008, Pimenta et al. 2011, MedlinePlus 2017).

B) Atropine is not listed by the EPA as an inert ingredient of toxicological concern.

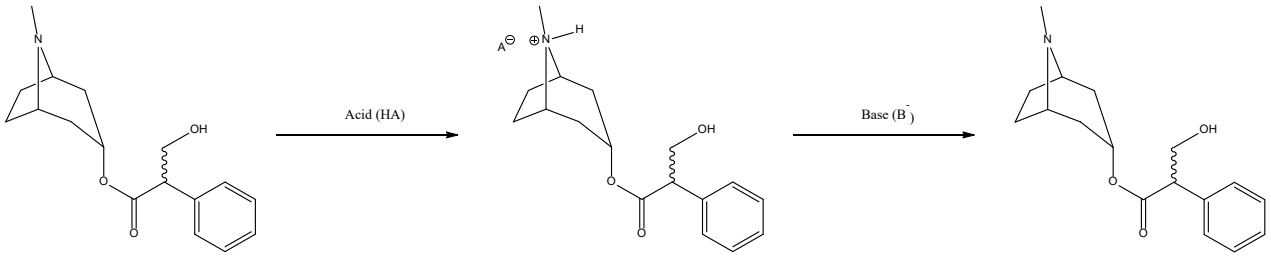
Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant,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

Atropine is a naturally occurring alkaloid produced by the plants in the nightshade family (EFSA 2008). The substance is biologically formed and exists exclusively of L-hyoscyamine in nature (missing the D-hyoscyamine enantiomer, which is also present in atropine) (PubChem 174174, Bunke et al. 1996, Reist et

al. 1997, EFSA 2008). Atropine is primarily isolated from *Atropa belladonna* as a racemic mixture (equal mixture of enantiomers) of D-hyoscyamine and L-hyoscyamine (D-hyoscyamine is not found in the initial biological sample and is produced during the isolation process) due to the low configurational stability of the benzyl stereocenter (Figure 1)) (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008).

Atropa belladonna roots are the primary biological source of atropine, which is isolated via extraction processes (Bensaddek et al. 2001, Dimitrov et al. 2005, EFSA 2008, al-Hemiri and Noori 2009). The extraction process is variable, but typically employs the extraction of the L-hyoscyamine alkaloid (a nitrogen-containing molecule that is produced in plants and is physiologically active) from ground *Atropa belladonna* roots with a basic aqueous solution (pH 8-10) (Dimitrov et al. 2001, EFSA 2008, al-Hemiri and Noori 2005, Timberlake 2015). The basic nature of the extraction maintains the neutral charge of the alkaloid by preventing protonation of the basic amine group on the bridgehead of the seven-membered tropyl ring (EFSA 2008). While L-hyoscyamine represents most of the isolated chemical substrate, other alkaloid structures (a nitrogen-containing molecule that is produced in plants and is physiologically active) are also present in the initial root extraction (Bensaddek et al. 2001, Timberlake 2015). Atropine is purified via subsequent extractions with organic solvents (e.g., chloroform, diisoproylether) to remove undesired chemical substrates (Bensaddek et al. 2001, Dimitrov et al. 2001, EFSA 2008, al-Hemiri and Noori 2009). During the extraction process from the initially enantiopure L-hyoscyamine present in the root, the benzyl stereocenter undergoes a racemization process (changes the three-dimensional configuration to the benzyl carbon) to yield the atropine mixture (a 1:1 ratio of D-hyoscyamine and L-hyoscyamine), which is isolated as the final product (*see* Figure 1 in Source or Origin of the Substance) (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008).

In some cases, the final step of the atropine extraction process includes an acidic treatment allowing for the isolation of an atropine salt from the organic solution (Equation 1) (Dimitrov et al. 2001, al-Hemiri and Noori 2009). The charged nature of the atropine salt dramatically reduces its solubility in organic solvents, allowing for collection of the salt as a solid. When acidic treatments are employed in the purification process, the isolated product must be treated with a base to regenerate the neutral from of atropine (Equation 1).



Equation 1

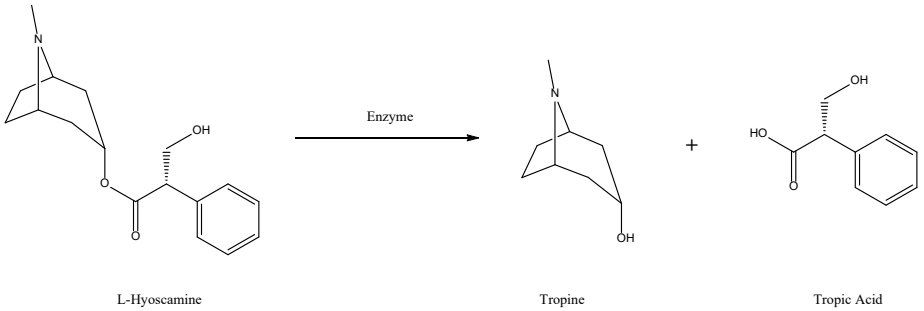
<u>Evaluation Question #3:</u> Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Atropine is a racemic mixture (equal mixture of enantiomers) of D-hyoscyamine and L-hyoscyamine alkaloids that is extracted from plants in the nightshade family, but only the L-hyoscyamine is biologically produced. (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008). During the extraction process, the L-hyoscyamine is racemized because the benzyl stereocenter has low configurational stability (Figure 1) (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008).

As discussed in Question #2, atropine is primarily extracted from the roots of *Atropa belladonna* via aqueous basic treatments, organic extractions, and isolation as a salt following acid treatment (Dimitrov et al. 2001, EFSA 2008, al-Hemiri and Noori 2009).

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

Atropine alkaloids are naturally produced by plants in the nightshade family, which exists exclusively (pre-extraction) as L-hyoscyamine (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008). Because L-hyoscyamine is the lone enantiomer that is biologically produced, atropine does not exist naturally, but rather is formed during the racemization of L-hyoscyamine to a 1:1 mixture of L-hyoscyamine and D-hyoscyamine (atropine) that takes place in the extraction process (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008). When absorbed by a range of animal species as a part of a veterinary treatment, the enantiomeric alkaloids present in atropine (D-hyoscyamine and L-hyoscyamine) are processed in different ways (EFSA 2008). Both enantiomers (the racemic atropine mixture) have relatively short biological half-lives, with both being excreted in urine in 2 – 5 hours (Williams et al. 2000, Aardema et al. 2008). However, the naturally produced L-hyoscyamine is largely hydrolyzed enzymatically to give excretion products of tropine and tropic acid (Equation 2) (EMEA 1998, EFSA 2008). The unnatural D-hyoscyamine formed during chemical extraction processes is excreted in-tact (EFSA 2008).



Equation 2

There are no reported studies on the persistence or concentration of atropine (neither D-hyoscyamine nor L-hyoscyamine) or the metabolized products tropine and tropic acid, although tropine has been identified as "readily biodegradable" (Sigma-Aldrich 2018b).

Due to the limited application of atropine (for veterinary medicine, approved for use only when used or ordered by a veterinarian), and the small quantities administered (milligrams), atropine is unlikely to be a source of environmental contamination (Rinaldi and Himwich 1954, Chugh et al. 2005, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). Moreover, the L-hyoscyamine enantiomer is largely degraded to tropine and tropic acid prior to excretion, further reducing the likelihood of environmental persistence and concentration build-up (Sigma-Aldrich 2018b).

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)).

Atropine is naturally produced by plants in the nightshade family, which exists exclusively pre-extraction as L-hyoscyamine and post-extraction, as a racemic mixture of L-hyoscyamine and D-hyoscyamine (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008). As described in the Characterization of Petitioned Substance section, atropine is a neurologically active compound that can cross the blood-brain barrier (Rinaldi and Himwich 1954, EMEA 1998, Eddleston et al. 2004, Eddleston et al. 2006, EFSA 2008). The antimuscarinic character of atropine relaxes smooth muscle tissue and inhibits excretions (Rinaldi and Himwich 1954, EFSA 2008). However, when over-applied, atropine poisoning may result with symptoms including abdominal pain, confusion and disorientation, hallucinations, urinary retention, hypothermia and tachycardia (Heath and Meredith 1992, Eddleston et al. 2006, Eddleston et al. 2008).

The toxicity of atropine is dependent on the species in question. The relative toxicity of atropine appears to be connected to the relative ability of the species to metabolize atropine to the less active tropine and tropic acid (Equation 2), typically catalyzed by atropine sterase enzymes (EFSA 2008). Studies have shown that rabbits, rats, guinea pigs, and poultry typically have these metabolizing proteins, making them particularly resistant to atropine toxicity (EFSA 2008). Previous studies have shown that cattle and pigs are the agriculturally most sensitive to atropine toxicity (Worthington et al. 1981, Nelson et al. 1982, Piva and Piva 1995, EFSA 2008). These studies were centered around feed samples contaminated with nightshade plants and extracts, rather than atropine itself, but since atropine is among the most prominent nightshade alkaloids, they offer some information on the susceptibility of these animals to atropine toxicity (EFSA 2008). These studies reported that relative to control groups, animals exposed to feeds contaminated with alkaloids had less weight gain or weight loss over the study period, with weight changes relying on the amount of alkaloid contamination in the feedstocks (Worthington et al. 1981, Nelson et al. 1982, Piva and Piva 1995).

When absorbed by a range of animal species, the enantiomeric alkaloids present in atropine (D-hyoscyamine and L-hyoscyamine) are processed in different ways (EFSA 2008). Both enantiomers (the racemic atropine mixture) have relatively short biological half-lives, with both being excreted in urine in 2 – 5 hours (Aardema et al. 2008). However, the naturally produced L-hyoscyamine is largely hydrolyzed enzymatically, producing tropine and tropic acid (Equation 2) (EMEA 1998, EFSA 2008). The unnatural D-hyoscyamine formed during chemical extraction processes is excreted in-tact (EFSA 2008).

There are no reported studies on the persistence or concentration of atropine (neither D-hyoscyamine nor L-hyoscyamine), or the metabolized products tropine and tropic acid, although tropine has been identified as "readily biodegradable" (Sigma-Aldrich 2018b). Tropine has also been identified as toxic to aquatic invertebrates, including *Daphnia magna* (water fleas) at concentrations of 54.7 mg/L (Sigma-Aldrich 2018b).

Due to the limited application of atropine (for veterinary medicine, approved for use only when used or ordered by a veterinarian), and the small quantities administered (milligrams), atropine is unlikely to be a source of environmental contamination or toxicity (Rinaldi and Himwich 1954, Chugh et al. 2005, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). Moreover, the L-hyoscyamine enantiomer is largely degraded to tropine and tropic acid prior to excretion, further reducing the likelihood of environmental persistence and concentration build-up (Sigma-Aldrich 2018b).

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

Atropine is approved for limited use in veterinary medicine (only when used or ordered by a veterinarian) and is administered in small quantities (milligrams) (Rinaldi and Himwich 1954, Chugh et al. 2005, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). Moreover, the L-hyoscyamine enantiomer is largely degraded to tropine and tropic acid prior to excretion, making the environmental persistence and concentration build-up of atropine unlikely (Sigma-Aldrich 2018b).

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)).

Due to the veterinary applications of atropine for approved organic use, it is unlikely to be combined with any of the acids explained below. Undesirable chemical reactions are unlikely to occur when used as approved, making environmental and human health concerns unlikely.

The alkaloid structure of atropine makes it an efficient base. As such, atropine will react with acids, resulting in an atropine salt with the cation being supplied by the acid used in the reaction (Equation 1). Due to the basic nature of the substance, it is likely to undergo neutralization reactions with allowed organic acids such as peracetic acid, ammonium carbonate, boric acid, humic acids, sulfurous acid (7 CFR 205.601), phosphoric acid and formic acid (7 CFR 205.603). Due to the ionic nature of the product (atropine

salt), with identity defined based on the acid used in the reaction (associated anion (A^- in Equation 1)), the effects of potential salts are difficult to predict.

Atropine salts (particularly atropine sulfate) are used for medicinal purposes, and atropine is likely to maintain its medicinal activity in salt forms (PubChem 174174, EMEA 1998, EFSA 2008). However, due to the charged nature of the salt, it may be absorbed differently from the neutral form, which could influence the biological delivery mechanisms.

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)).

There are no reported studies on how atropine (D-hyoscyamine or L-hyoscyamine) interacts with its environment, including the relevant soil systems, soil organisms, and crop production.

As discussed in Question #5, atropine is a neuralgically active substance capable of producing toxic outcomes when absorbed. However, the susceptibility of atropine toxicity is highly species dependent (Worthington et al. 1981, Nelson et al. 1982, Piva and Piva 1995, EFSA 2008). When atropine is absorbed in amounts that result in atropine poisoning, symptoms may include abdominal pain, confusion and disorientation, hallucinations, urinary retention, hypothermia and tachycardia, with fatalities possible at high concentrations (Heath and Meredith 1992, Eddleston et al. 2006, Eddleston et al. 2008).

Due to the limited application of atropine (for veterinary medicine, approved for use only when used or ordered by a veterinarian), and the small quantities administered (milligrams), atropine is unlikely to have a negative impact on livestock or the agrosystem (Rinaldi and Himwich 1954, Chugh et al. 2005, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). Moreover, the L-hyoscyamine enantiomer is largely degraded to tropine and tropic acid prior to excretion, further reducing the likelihood of unintended ingestion/absorption by livestock and environmental persistence and concentration build-up (Sigma-Aldrich 2018b).

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

There is little to suggest that atropine poses a threat to the environment when used as approved. There are no reported studies on the persistence or concentration of atropine (D-hyoscyamine or L-hyoscyamine), or the metabolized products tropine and tropic acid, although tropine has been identified as "readily biodegradable" (Sigma-Aldrich 2018b).

Due to the limited application of atropine (for veterinary medicine, approved for use only when used or ordered by a veterinarian), and the small quantities administered (milligrams), atropine is unlikely to be a source of environmental contamination (Rinaldi and Himwich 1954, Chugh et al. 2005, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). Moreover, the L-hyoscyamine enantiomer is largely degraded to tropine and tropic acid prior to excretion, further reducing the likelihood of environmental persistence and concentration build-up (Sigma-Aldrich 2018b).

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)).

Atropine is a racemic mixture of the naturally occurring alkaloid L-hyoscyamine found in plants of the nightshade family (PubChem 174174, Bunke et al. 1996, Reist et al. 1997, EFSA 2008). As discussed in Question #5, the atropine is a neurologically active substance, and its alkaloidal structure allows atropine to cross the blood-brain barrier to provide physiological responses following its absorption (Rinaldi and Himwich 1954, EMEA 1998, Eddleston et al. 2004, Eddleston et al. 2006, EFSA 2008).

Atropine is used in both human and veterinary medicine, largely to achieve the same effects. Atropine employs the same antimuscarinic mode of action in humans and livestock when used as a treatment for organophosphate poisoning by competition with acetylcholine for neurological binding sites (Rinaldi and Himwich 1954, EMEA 1998, Robenshtok et al. 2002, Eddleston et al. 2005, Eddleston et al. 2006, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010). The resulting relaxation of smooth muscles and inhibition of secretions aids the effectiveness of subsequent treatments (e.g., oximes, oxygenation) and relieves the cholinergic symptoms of organophosphate poisoning (Rinaldi and Himwich 1954, Kassa 2002, Eddleston et al. 2004, Chugh et al. 2005, Eddleston et al. 2006, Eddleston et al. 2008). However, atropine treatments are not well-defined, with the effective quantity of atropine administration relying on the exposure levels to the organophosphate poison (Kassa 2002, Eddleston et al. 2004, Eddleston et al. 2008). When used as an organophosphate treatment, atropine levels are increased until cholinergic symptoms dissipate, or symptoms of atropine toxicity are observed (Rinaldi and Himwich 1954, Eddleston et al. 2004, Eddleston et al. 2006, Aardema et al. 2008, Eddleston et al. 2008).

Atropine is most commonly administered intravenously, although it may also be also be applied via ingestion, or ocular absorption (applied directly to the eye) (EMEA 1998, Williams et al. 2000, Eddleston et al. 2004, Chugh 2005, Flomenbaum et al. 2006). Intravenous administration of the substance using proper medical protocols (e.g., gloves, premeasured doses) makes inadvertent human absorption unlikely. Due to the neurophysiological profile of atropine, its absorption also poses toxicological concerns. Atropine intoxication is associated with symptoms including abdominal pain, confusion and disorientation, hallucinations, urinary retention, hypothermia and tachycardia (Heath and Meredith 1992, Eddleston et al. 2006, Eddleston et al. 2008). Atropine toxicity can be lethal in humans, however, the level of toxicity and its relationship to fatal outcomes is not well defined. This likely depends on the unique neurochemical profile of the individual, much like atropine quantities for poison treatments are dependent on the neurochemical profile created by the level of poison exposures. In clinical applications, the fatal dosage of atropine in some patients has been documented as low as 10 mg, while other patients have survived 1000 mg dosages (Brunton et al. 2006).

Atropine is also used in human ophthalmology for pupil dilation, and to relieve ocular pain and inflammation (MedlinePlus 2017). The mode of action for the human ophthalmic applications follow the same mode of action as its veterinary applications, where the desired outcomes are primarily due to the relaxation of smooth muscles and inhibition of secretions brought about by competition with choline neurotransmitters (EMEA 1998, Herring et al. 2000, Williams et al. 2000, MedlinePlus 2017). The ability of atropine to inhibit secretions (e.g., sweat, saliva) based on its anticholinergic response makes it a useful active ingredient in over-the-counter (OTC) cold medicines (Mayo Clinic 2017). These inhibitory responses alleviate mucus accumulation, producing a drying effect in the nose and chest (Mayo Clinic 2017).

The metabolism of atropine in humans is like that of most animal species. Atropine is both readily absorbed and distributed within the human body and readily excreted in urine (EMEA 1998, Williams et al. 2000, Aardema et al. 2008, EFSA 2008). Similar to the metabolic pathways in veterinary applications, humans also metabolize L-hyoscyamine (one enantiomer of the racemic atropine mixture) to tropine and tropic acid (Equation 2), which are excreted in urine along with the non-metabolized D-hyoscyamine enantiomer present in atropine (EMEA 1998, EFSA 2008). The short biological half-life of atropine (2-5 hours), and incorporation of the substance in human medical applications makes negative health effects from the approved usage of atropine unlikely (Williams et al. 2000, Aardema et al. 2008, Mayo Clinic 2017, MedlinePlus 2017). Moreover, atropine is approved for use only when used or ordered by a veterinarian, and the short biological half-life of atropine, coupled with the withdrawal restrictions placed on animals receiving atropine treatments makes human health effects unlikely (Rinaldi and Himwich 1954, Chugh et al. 2005, Aardema et al. 2008, Eddleston et al. 2008, Kumar et al. 2010).

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)).

The primary application of atropine within veterinary medicine for organic livestock production is the treatment of organophosphate poisoning. Atropine is recognized as the most efficient treatment option for organophosphate poisoning within both human and veterinary medicine (WHO 1999, Robenshtok et al. 2002, Eddleston et al. 2006, Eddleston et al. 2008, Kumar et al. 2010). This determination has made the administration of atropine a standard treatment procedure for organophosphate poisoning, although in some clinical applications, the application of oximes as a cotreatment or as a subsequent treatment is also prescribed (Karalliedde 1999, WHO 1999, Kassa 2002).

Magnesium sulfate ($MgSO_4$) is approved for use in organic livestock production at 7 CFR 205.603, and is being studied as a potential alternative or additional treatment to atropine administration for organophosphate treatment protocols (Feldman and Karalliedde 1996, Singh et al. 1998, Eddleston et al. 2006). Magnesium sulfate is believed to induce an anticholinergic response through inhibiting the release of acetylcholine into the neural synapse (Feldman and Karalliedde 1996, Singh et al. 1998). Despite the promising application of magnesium sulfate as an organophosphate treatment, it has seen little clinical applications, and more studies are required to evaluate its effectiveness compared to traditional atropine and atropine oxime combination treatments (Eddleston et al. 2006).

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

As described in Question #11, the main veterinary application of atropine is organophosphate treatment. Atropine is recognized as the most efficient treatment option for organophosphate poisoning within both human and veterinary medicine (WHO 1999, Robenshtok et al. 2002, Eddleston et al. 2006, Eddleston et al. 2008, Kumar et al. 2010). As these livestock poisoning events are accidental and may arise from a range of possible scenarios including organophosphate contamination from a neighboring environment there are no alternative practices that make the medical applications of atropine unnecessary.

There are several natural anesthetics that can be used in place of atropine. These substances include willow bark, the natural source of the common analgesic aspirin (Goldberg 2009, Healthline 2017). Moreover, wintergreen and its oils act as a natural analgesic due to the presence of methyl salicylate (a substance similar in nature to aspirin) (Flomenbaum et al. 2006). Cloves have also been reported to provide topical pain relief and treat toothaches, with performance comparable to benzocaine (Alqareer et al. 2006, Healthline 2017). Additionally, the natural spice turmeric contains the compound curcumin that has been reported to relieve pain and inflammation (Healthline 2017).

Report Authorship

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

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