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ATROPINE
Livestock

Executive Summary

Atropine is an anti-cholinergic drug that is derived from the plant *atropa belladonna.* It is not found in its natural alkaloid form alone, but rather as a racemic mixture with hyoscyamine. As such, it is synthetically manufactured for commercial veterinary purposes. It is commonly used as an antidote for organophosphate poisoning but it is also used as an antispasmodic, mydriatic, anti-cholinergic, and blocker of vagal induced bradycardia and brochospasm.

Farmers are petitioning its use as the antidote for organophosphate poisoning usually caused by reactions to pesticides. It is administered orally by a licensed veterinarian in cases where poisoning is suspected and it is a benign treatment without a holistic or natural alternative.

According to the final ruling by the OFPA, there is no real prohibition of atropine specifically stated although there are particular restraints for all antibiotics in general. There are no specific rulings against or in favor of antidotes in general. It is assumed that it is considered a general antibiotic. If considered for its anesthetic properties, the ruling is again a general one.

Summary of TAP Reviewer's Analyses[1]

Synthetic/ Nonsynthetic	*Allow without restrictions?*	*Allow only with restrictions? (See Reviewers' comments for restrictions)*
Synthetic (2) Nonsynthetic (1)	Yes (1) No (2)	Yes (1) No (2)

Identification

Chemical names: Atropine, $C_{17}H_{23}NO_3$ [2]

[1] *This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(M) of the OFPA [7 USC 6517(m)]. The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other factors that the NOSB and the USDA may want to consider in making decisions.*

[2] CHEMID Plus *Atropine*
http://chem.sis.nlm.nih.gov/chemidplus/results.html?bNewSearch=true&beginRec=1&outStruct=molstructure&endRec=5&haveReadyQuery=T&readyQuery=TBL_NUMBER(+TBL_NUMBER%3EMEMDATAUPR%3D+'101-31-5'+OR++TBL_NUMBER%3EMEMDATAUPR%3D+'51-55-8')

NSRDS-NBS-63)
Intense mass spectral peaks: 83 m/z, 94 m/z, 124 m/z, 140 m/z, 289 m/z

Other Chemical/Physical Properties: colorless crystals or white crystalline powder;
Odorless;
Effloresces in dry air;
When dried at 120°C for 4 hours, it melts at a temperature not below 187°C;
Aqueous solution is neutral or faintly acidic to litmus paper;
Sublimes in high vacuum at 93-110°C;
NMR: 9889

Fire Potential: Slight

Stability/Shelf Life: Sensitive to light
Slowly affected by light

How Made:

Atropine is found with hyoscyamine in the deadly nightshade plant *atropa belladonna*. Hyoscyamine is optically active, $[a]_D$ -22° but readily hydrolyses to atropine on hydrolysis in aqueous alcohol.

The Plant, *atropa belladonna* has brown-purple flowers and berries which change from red to purple as the summer progresses:

[6]

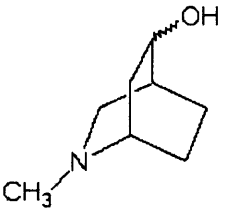
Synthetically, it was first made in 1901, by reacting tropine with tropic acid:

Making of tropine:

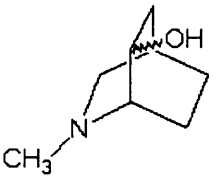
Tropic acid was shown to have a molecular formula of $C_9H_{10}O_3$ and lost a molecule of water to yield atropic acid on strong heating. Atropic acid, $C_9H_8O_2$, had the structure (1) implying that tropic acid was either: compound (2) or (3):

[6] *Atropine* http://www.chm.bris.ac.uk/motm/atropine/source.htm

Since tropinic acid is a dicarboxylic acid and no carbon is lost in the oxidation, the alcohol group oxidation must have involved ring cleavage and so the hydroxyl group had to be within a ring. This made the Ladenburg structures untenable and so Merlin proposed either structure (6) or (7) for tropine:

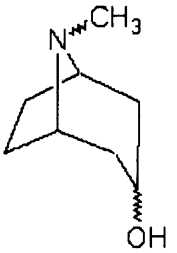


(6)



(7)

Willstätter (1895 - 1891) notes that tropinone was formed during oxidation prior to ring cleavage. This substance was a ketone which was demonstrated to contain the CH_2COCH_2 moiety by the formation of dibenzylidene and di-oximino derivatives. This, in turn, made Merling's structures untenable and so Willstätter proposed structure (8) for tropine:

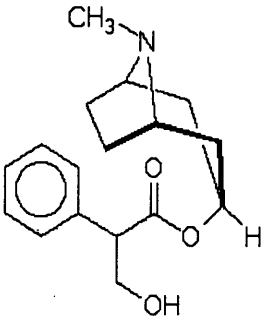


(8)

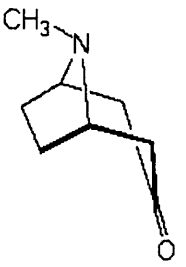
The structure of tropine has been confirmed to be (8) by synthesis by Willstätter (1900 - 1903) and by Robinson (1917)[7]

Making of atropine, by combining tropine with tropic acid:

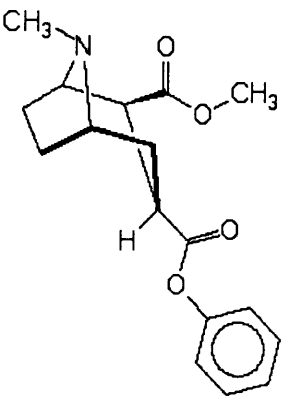
[7] *Atropine* http://www.chm.bris.ac.uk/motm/atropine/strucuture.htm



Atropine (1)

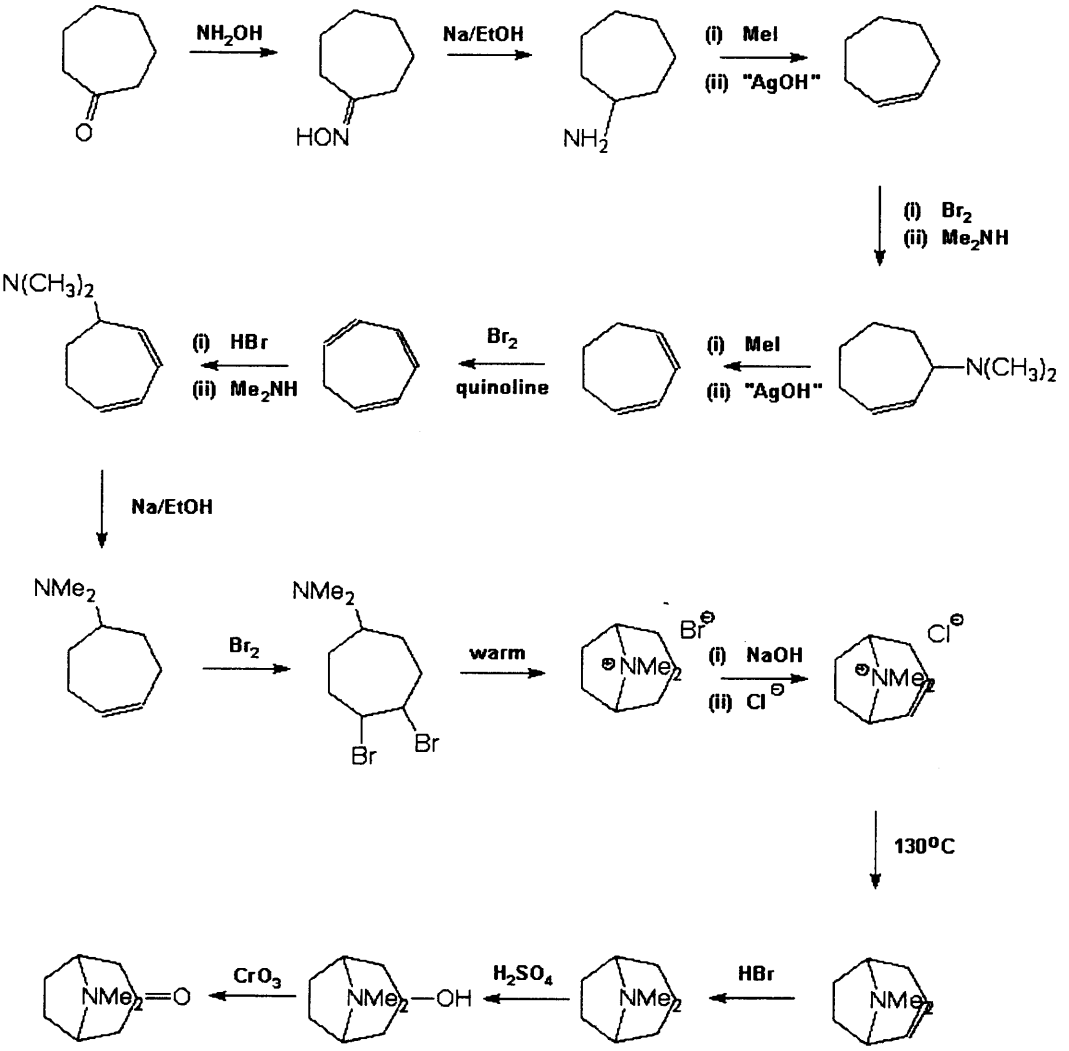


Tropinone (2)



Cocaine (3)

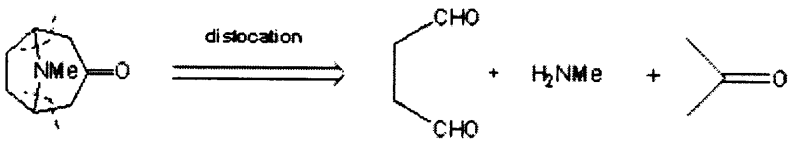
It was relatively straightforward to reduce tropinone to tropine and hence form its ester atropine.



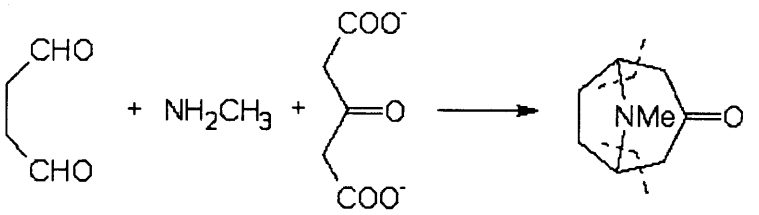
The preparation of tropinone is a competent but long synthesis which demonstrates one of the fundamental difficulties involved in the preparation of complex organic molecules. Although the individual steps in the synthesis generally give good to excellent yields, there are many of them which means that the overall yield becomes diminishingly small, of the order of 1%. As a result the early steps in the synthesis have to be carried out on inconveniently large quantities of material, and despite this, usually have to be repeated several times in order to obtain sufficient material to carry out the later stages on an acceptable scale.

In 1917 Robinson approached the synthesis in a totally radical way. In his own words:

> The initial product is a salt of tropinone dicarboxylic acid, and this loses two molecules of carbon dioxide with the formation of tropinone when the solution is acidified and heated".



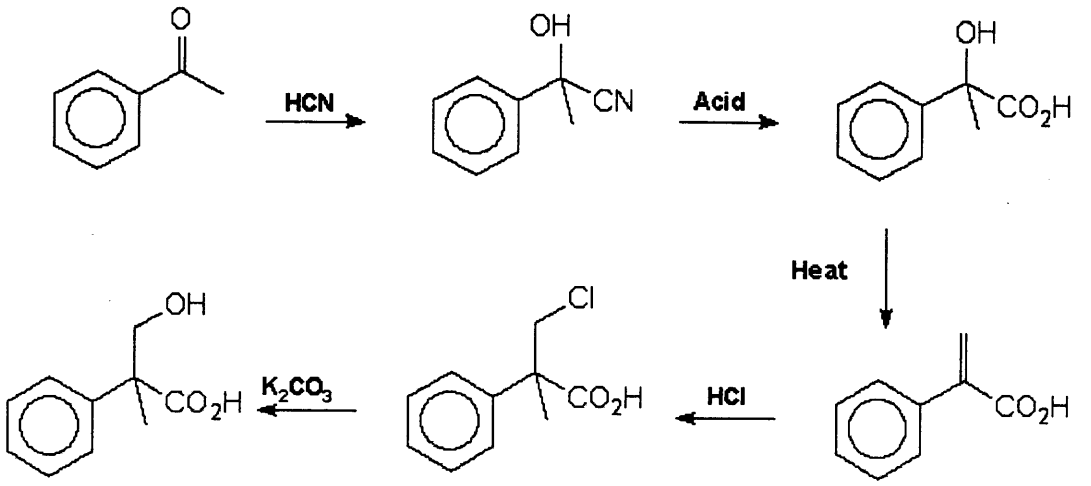
This resulted in the formation of tropinone in one step. More recent work has allowed the yield for this reaction to be raised to about 90%, mainly by carrying out the processed under buffered conditions.



Tropinone may then be converted into tropine by metal in acid reduction, the best yields being obtained using zinc in HI. It may be noticed that the final precursor in the Willstätter synthesis appears to be tropine. This is not the case as the material is its geometric isomer, *j* -tropine, and thus tropine is formed by oxidation of *j* -tropine to tropinone followed by stereoselective reduction of the carbonyl group.

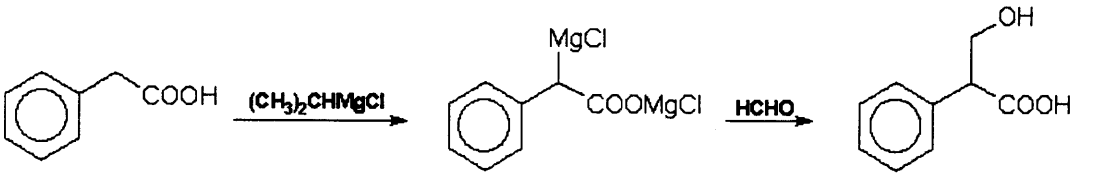
Tropic acid

Mackenzie and Ward proved the structure of tropic acid by synthesis from acetophenone in 1919:



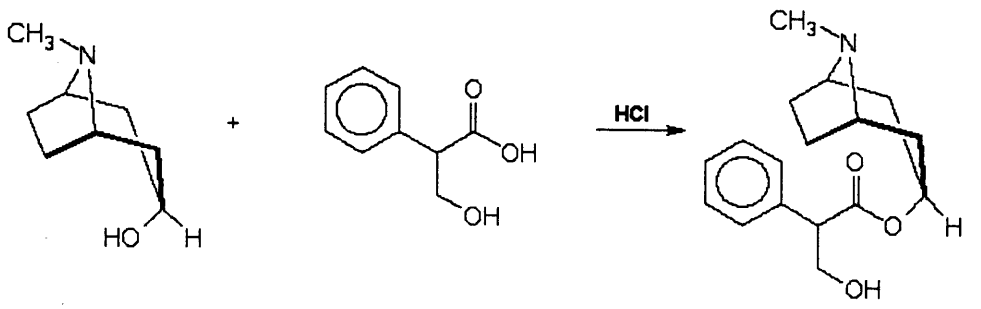
Note that the addition of HCl in step 4 contravenes Markownikoff's rule. This is presumably due to the electron withdrawing effect of the carboxyl group which destabilises the tertiary carbonium ion intermediate relative to the primary carbonium ion. It is tropic acid which introduces the stereocenter into the atropine molecule. The racemic mixture formed from this reaction sequence may be resolved by reaction with quinine followed by fractional crystallisation of the diastereoisomers.

More recently Blicke *et al* have prepared tropic acid from phenylacetic acid via a Grignard reagent and formaldehyde:



Atropine

The final problem in the synthesis, the combination of tropine and tropic acid, was overcome by a Fischer-Speier esterification. The acid and alcohol were heated together in the presence of HCl to yield atropine



Atropine [8]

Specific Uses:

Atropine comes in various forms, including an oral tablet, and is found in many combination medications, including some diarrhea medications, cold or cough medications, and antispasmodic medications; it has been used in the past as "Belladonna" to give women a wide-eyed appearance, due to its ability to dilate the pupil (which also causes the blurry vision side effect).[9]

The names atropine and belladonna both relate to this drug complex's effects. The former is derived from Atropos -- one of the three fates in Greek mythology -- as a result of its being used as a poison during the Middle Ages. The latter refers to its ability to dilate the eyes of "beautiful ladies." Both are used nowadays in medicine as an antispasmodic, especially for parkinsonism, with an average dose of atropine being 0.5 mg. users have survived dosages of more than a gram, but the effects appear toxic in most cases of 10 mg. or more.[10]

Atropine is a classic example of the cholinergic blockers. It is found alone and in combination with a wide-variety of other drugs. As an ophthalmic preparation (Isopto-Atropine®), it is used as a cycloplegic and as a mydriatic. Side effects associated with the use of atropine are unsteadiness, hallucinations, unusual dryness of mouth, and increased sensitivity of eyes to light. Patients who have glaucoma should use caution when using this preparation. [11]

Atropine is the most essential drug in the treatment of nerve agent poisoning. It combats the effect of the nerve agent in the airways. Atropine reduces secretions and relieves the narrowing of the airways that may otherwise result in choking to death.[12]

Atropine is still used as a premedication for anesthesia. Its effect in the inhibition of salivary and bronchial secretions makes it very useful during surgery, with the risk of secretions blocking airways being reduced. Similarly, the relaxation effect on bronchial smooth muscle again reduces the risk of airway obstruction.

Atropine also prevents the bradycardia that can be produced with some anesthetic agents such as suxamethonium. In ophthalmology, atropine is still used. Its ability to dilate the pupil and also paralyze the eyes, makes it a useful compound to have whilst treating inflammatory conditions of the eye.[13]

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[8] *Atropine* http://www.chm.bris.ac.uk/motm/atropine/synthesis.htm
[9] *Pharmacologic Treatments: Atropine* http://www.droolinginfo.org/pharma.html
[10] *Belladonna-like Substances* http://www.erowid.org/plants/datura/datura_info1.shtml
[11] *EXAMPLES OF CHOLINERGIC BLOCKING AGENTS* http://www.sweethaven.com/academic/lessons/pharmacol01/module021004.htm
[12] *Atropine & HI-6 Auto-injector* http://www.dnd.ca/health/hs_staff_sites/med_info_sheets/engraph/Info_Sheet_AtrHI6_final_e.asp
[13] *Deadly Night Shade* http://www.portfolio.mvm.ed.ac.uk/studentwebs/session2/group13/deadnight.html

ATROPINE IS USUALLY EMPLOYED IN FORM OF ITS SULFATE SALT.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975. 840]**PEER REVIEWED**

ATROPINE IS USED AS ANTIDOTE FOR PILOCARPINE, PHYSOSTIGMINE, ISOFLUROPHATE, CHOLINE ESTERS, CERTAIN SPECIES OF AMINATA, & IN...ANTICHOLINESTERASE INSECTICIDE POISONING.
[American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984.,p. 12:08]**PEER REVIEWED**

PT POISONED BY ORG PHOSPHORUS COMPD OR CARBAMATES ARE TOLERANT TO **ATROPINE** & CAN RECEIVE LARGE DOSES. ... PT SHOULD BE KEPT ON VERGE OF **ATROPINE** INTOXICATION.
[Hayes, W. J., Jr. Toxicology of Pesticides Baltimore: Williams & Wilkins, 1975. 409]**PEER REVIEWED**

/USED TO RELIEVE/...HYPERMOTILITY OF COLON...TO RELAX SPASM OF BILIARY & URETERAL COLIC, & BRONCHIAL SPASM...USED TO CONTROL CRYING & LAUGHING EPISODES IN PT WITH BRAIN LESIONS &...CLOSED HEAD INJURIES WHICH CAUSE ACETYLCHOLINE TO BE RELEASED...
[American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984.,p. 12:08]**PEER REVIEWED**

...CENTRAL ACTION IS EMPLOYED IN TREATMENT /PRC- LARGELY REPLACED BY L-DOPA/ OF PARKINSONISM IN WHICH RIGIDITY & TREMOR ARE RELIEVED. ... **ATROPINE** IS USED PRINCIPALLY FOR ITS SPASMOLYTIC EFFECT ON SMOOTH MUSCLE...SPASMOLYTIC EFFECT IN EYE TO PRODUCE DILATATION...TO RELIEVE PYLOROSPASM, HYPERTONICITY OF SMALL INTESTINE...
[American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984.,p. 12:08]**PEER REVIEWED**

...**ATROPINE** IS...POTENT /ANTIMUSCARINIC AGENT/ ON HEART, INTESTINE, & BRONCHIAL MUSCLE, & HAS...PROLONGED ACTION. ...DOES NOT DEPRESS CNS IN CLINICAL DOSES...
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 517]**PEER REVIEWED**

MEDICATION (VET): ...USED ROUTINELY AS ADJUNCT TO GENERAL ANESTHESIA...TO DECR SALIVARY & AIRWAY SECRETIONS. ... USED TO FACILITATE OPHTHALMOSCOPIC EXAM OF INTERNAL OCULAR STRUCTURES & FUNCTIONS &...FOR TREATMENT OF VARIOUS OCULAR DISORDERS. ... **ATROPINE** IS ESSENTIAL ANTIDOTE TO ANTICHOLINESTERASE OVERDOSAGE & POISONING.
[Jones, L.M., et al. Veterinary Pharmacology & Therapeutics. 4th ed. Ames: Iowa State University Press, 1977. 159]**PEER REVIEWED**

ATROPINE MAY BE USED TO ANTAGONIZE PARASYMPATHOMIMETIC EFFECTS OF NEOSTIGMINE OR OTHER ANTI-CHE AGENTS ADMIN IN TREATMENT OF MYASTHENIA GRAVIS.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 531]**PEER REVIEWED**

Atropine may be of value in the initial treatment of carefully selected patients with acute myocardial infarction in whom excessive vagal tone causes sinus or nodal bradycardia accompanied by a falling blood pressure and a low cardiac output or a high grade A-V block resulting in ectopic ventricular tachyarrhythmia.

Atropine is a specific antidote for the so-called rapid type of mushroom poisoning due to the cholinomimetic alkaloid muscarine found in Amanita muscaria and a few other fungi [GOODMAN. PHARM BASIS THERAP 7TH ED 1985 p.143]**PEER REVIEWED**[14]

Action:
Atropine Sulfate Oral: Nerve impulses are transmitted to muscles and glands throughout the body by the action of specialized, naturally occurring chemicals known as neurotransmitters. Atropine blocks the ability of the neurotransmitter acetylcholine to stimulate certain muscles and glands. This produces effects ranging from drying of secretions (saliva, perspiration) to changing the size of the pupils and relief of intestinal muscle spasms.[15]

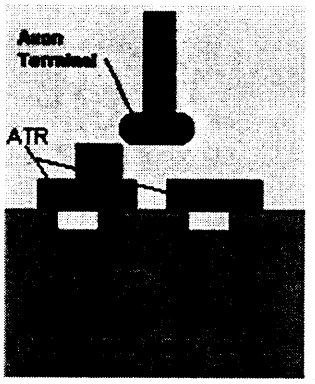
The atropine eye drop works by temporarily blurring vision in the unaffected eye, thereby forcing the eye with amblyopia to be used. This strengthens the eye and improves vision. A parent simply places a drop in the child's eye once a day. With patching, a parent must monitor the child for at least six hours each day for many weeks or months.

Atropine works by blocking one type of acetylcholine receptor so that the acetylcholine that is already in the synapse cannot work:

Acetylcholine in the presence of a nerve agent

ACh = Acetylcholine
E = Acetylcholinesterase

ATR = Atropine



1. ACh is released at the axon terminal.
2. ACh crosses the synaptic cleft.
3. ACh binds with a receptor on the post-synaptic membrane.
4. Nerve agents (NA) block the ability of AChE to stop the action of ACh.
5. Atropine blocks the receptor so that ACh cannot work. Note that there is NO direct effect on the nerve agent or AChE.

[16]

Combinations:
In an analysis done on serotonin, it was found that serotonin will constrict the airways of cattle in a dose-related fashion. This constriction can be blocked by a serotonin antagonist called cyproheptadine. The pattern of blockade is typical of that seen when the agonist (serotonin) interacts directly with a specific receptor. It has been suggested that at least part of the effect in other species is indirect through a

[14] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2
[15] *Atropine Sulfate Oral* http://www.wholehealthmd.com/refshelf/drugs_view/0,1524,43,00.html#How_It_Works
[16] *Eye Drops to Treat Childhood Eye Disorder Works As Well as Patching the Eye* http://www.cincinnatichildrens.org/About_us/News_Media/News_Releases/2002/0313-drops-eye-disorder.htm

cholingeric receptor. Atropine, which blocks cholingeric receptors, was added to the organ bath either alone or in combination with cyproheptadine prior to the addition of serotonin. Cyproheptadine blocked 45% of the constriction, atropine 22%, and atropine and cyproheptadine blocked 60%. This data suggested that serotonin has both a direct and indirect effect through serotonin receptors and indirect through cholinergic receptors. [17]

In cases of cholinesterase inhibition, atropine by injection is antidotal. 2-PAM (Protopam Chloride) is also antidotal when administered early and in conjunction with atropine. If cholinesterase inhibition is suspected, atropine by injection is antidotal after cyanosis is relieved. Pralidoxime chloride (2-PAM) is also antidotal when given early, and in conjunction with atropine. Never use morphine. Close supervision of the patient is indicated for 48-72 hours.[18]

The Atropine Sulfate Injection, USP, is a sterile, nonpyrogenic isotonic solution of atropine sulfate monohydrate in water for injection with sodium chloride sufficient to render the solution isotonic. It is administered parenterally by subcutaneous, intramuscular, or intravenous injection. Atropine is a naturally occurring belladonna alkaloid which exists as a racemic mixture of equal parts of d- and l-hycocyamine, whose activity if due most entirely to the levo isomer of the drug.[19]

Diphenoxylate and Atropine combined make a drug called *Lomotil*, which is used to fight diarrhea in humans. It is noted that this combination of diphenoxylate and atropine should NOT be used in combination with other drugs such as isocarboxazid, phenelzine, and tranylcypromine, which are collectively known as MAO inhibitors. It should also be used cautiously when the patient is already taking narcotic cough or pain relievers, and sleeping pills, tranquilizers, or muscle relaxants.[20]

When used as premedication for anesthesia, atropine decreases bronchial and salivary secretions, blocks the bradycardia associated with some drugs used in anesthesia such as halothane, suxamethonium, and neostigmine, and also helps prevent bardycardia from excessive vagal stimulation.

During reversal of neuromuscular blockade in adults 1-1.2mg of atropine is given mixed with 2.5-5mg neostigmine.[21]

Atropine has often been given with an opioid in the treatment of renal colic
[GOODMAN. PHARM BASIS THERAP 7TH ED 1985 p.143]**PEER REVIEWED**

The belladonna alkaloids /**atropine**/ were often used prior to the administration of a general anesthetic agent, mainly to inhibit excessive salivation and secretions of the respiratory tract; their concomitant bronchodilator action is also of value.[22]

Status

Historic Use by Organic Farmers:

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[17] *The Role of Mediators Released From Cells in Pneumonia of Cattle* http://131.104.112.18/beefupdate/articles96/a-role_of_mediators_released_from_.htm
[18] *Material Safety Data Sheet* http://216.239.51.100/search?q=cache:x3hIHi0KI2sC:www.pbigordon.com/product_msds_turf/Pre-San_12-5G_MSDS.pdf+EPA+and+atropine&hl=en&ie=UTF-8
[19] *Atropine – RxList Monographs* http://www.rxlist.com/cgi/generic3/atrop.htm
[20] *Medication Information Sheet from The Cheshire Medical Cente: Diphnoxylate with Atropine (Lomotil)* http://www.cheshire-med.com/services/pharm/meds/diphenoxylate_with_atropine.html
[21] Practical Procedures: *Atropine* http://www.nda.ox.ac.uk/wfsa/html/u06/u06_017.htm
[22] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2

Atropine often is used as a pre-anesthetic and also is an antidote for organophosphate intoxication. There are no FDA-approved formulations of atropine for any species, but there are injectable prescription products marketed under 21 CFR 500.55, which is an exemption from certain drug labeling requirements.[23]

When Optem Duo Termiticide (a pesticide), is ingested, atropine tablets are to be given every fifteen minutes until the mouth dries in addition to induced vomiting using Ipecac syrup APF.[24]

Administration of atropine to dairy cows can lower circulating levels of amino acids and reduce concentrations of milk protein, without affecting milk fat yield or blood glucose levels (Prosser and McLaren, 1997). Atropine may therefore be useful for reducing circulating levels of blood amino acids to base levels during studies designed to elucidate the effects of perturbations of blood amino acid profile on milk protein composition. The current experiment was designed to evaluate the effect of varying doses of atropine on concentrations of protein, casein and selected proteins in milk.[25]

Ovine: Not routinely used as pre-anesthetic.[26]

Bovine, Ovine, Caprine, and Swine: It has been suggested that use of atropine as an antisialagogue is of little value because it does not reduce the amount of saliva secreted. Rather, atropine causes an increase in saliva viscosity, rendering it more difficult to remove from the respiratory passages if inhaled. However, the use of anticholinergics to treat or prevent bradycardia is effective.[27]

OPtimizer is a molded plastic cattle ear tag containing diazinon. Diazinon is an organophosphate insecticide. If symptoms of cholinesterase inhibition are present, atropine sulfate by injection is antidotal. 2-PAM is also antidotal and may be administered, but only in conjunction with atropine.[28]

Camelids: Atropine and glycopyrrolate:

a. Not used routinely because ileus potentiates bloat and cattle are slow to resume eating after anesthesia.

b. Atropine premed may be advisable in Llamas because some may develop bradycardia abruptly during anesthesia.[29]

Equine: Atropine has been used commonly as an adjunct for treatment of uveitis. The mydriatic effect of atropine may persist for a week or longer, even after it is discontinued. Mydriasis can increase intraocular pressure by partially closing the iridocorneal angle. Because of this, tropicamide may be safer than atropine for use in uveitis. Tropicamide has the same beneficial effects as atropine, yet its duration of action is much less. If intraocular pressure rises after mydriasis, the effects of tropicamide will diminish within a day.[30]

OFPA, USDA Final Rule:

OFPA states in Sec. 6509(d):

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[23] *Extralabel use of tranquilizers and general anesthetics* http://www.farad.org/vets/digest4.html

[24] *Material Safety Data Sheet: Optem Duo Termiticide* http://pct.au.com/msds/optem_pre_msds.pdf

[25] *Effects of Atropine on the Concentration and Composition of Milk Proteins in Dairy Cows* http://www.bsas.org.uk/publs/milkcomp/29.pdf

[26] *Ovine Formulary* http://www.cvm.umn.edu/smallruminant/Files/Ovine%20formulary.htm

[27] Veterinary Medicine: Oklahoma State University. *Species: Ruminants and Swine.* http://www.cvm.okstate.edu/courses/vmed5412/Lect18.asp

[28] *Insecticide Cattle Ear Tag.* http://216.239.51.100/search?q=cache:jP12AJPG9MIC:www.y-tex.com/pdfs/OPtimizer.PDF+atropine+in+cattle&hl=en&ie=UTF-8

[29] *ANESTHESIA AND ANALGESIA IN RUMINANTS* http://lam.vet.uga.edu/LAM/LM000087.HTML#7.Atropine%20and%20glycopyrrolate

[30] http://www.veterinaryvision.com/dvm_forum/dvm-equine.htm

(d) **Health Care.**

(1) **Prohibited Practices.** For a farm to be certified under this chapter as an organic farm with respect to the livestock produced by such farm, producers on such farm shall not

(A) use subtherapeutic doses of antibiotics;

(B) use synthetic internal paraciticides on a routine basis; or

(C) administer medication, other than vaccinations, in the absence of illness. [31]

Atropine is found as a racemic mixture with hyoscamine in the deadly nightshade plant *atropa belladonna.* It is also synthetically obtained and is used primarily in cattle that are suffering from Organophosphate poisoning. Administered by a licensed practitioner, atropine is generally given orally.

Policies from the FDA:

Note: The following law pertains to the use of chlorofluorocarbon propellants in self-pressurized containers. Relevant information has been highlighted and italicized from the text.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 2--GENERAL ADMINISTRATIVE RULINGS AND DECISIONS--Table of Contents

Subpart G--Provisions Applicable to Specific Products Subject to the Federal Food, Drug, and Cosmetic Act

Sec. 2.125 Use of chlorofluorocarbon propellants in self-pressurized containers.

(a) As used in this section:

(1) Chlorofluorocarbon means any fully halogenated chlorofluoroalkane.

(2) Propellant means a liquefied or compressed gas that is used in whole or in part to expel from the same self-pressurized container or from a separate container a liquid or solid material different from the propellant, but the term does not include the use of a chlorofluorocarbon as an aerating agent for foamed or sprayed food products.

(b) Chlorofluorocarbons are widely used in products subject to the Federal Food, Drug, and Cosmetic Act, with the principal use being as propellants in self-pressurized containers. Information recently developed indicates that chlorofluorocarbons may reduce the amount of ozone in the stratosphere and thus increase the amount of ultraviolet radiation reaching the earth. An increase in ultraviolet radiation may increase the incidence of skin cancer, change the climate, and produce other effects of unknown magnitude on humans, animals, and plants. Chlorofluorocarbons may also affect the climate by increasing infrared absorption in the atmosphere.

(c) Except as provided in paragraph (e) of this section, any food, drug, device, or cosmetic in a self-pressurized container that contains

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[31] *6509 Animal Production Practices and Materials.* Federal Organic Food Production Act of 1990. http://www.ams.usda.gov/nop/orgact/htm

a chlorofluorocarbon propellant is adulterated and/or misbranded in violation of the act, and any drug product in a self-pressurized container that contains a chlorofluorocarbon propellant is a new drug or a new animal drug.

(d) The use of a chlorofluorocarbon as a propellant in a self-pressurized container of a drug product will not result in the drug product being adulterated and/or misbranded provided a new drug application, a new animal drug application, or in the case of a certifiable antibiotic an antibiotic application for the drug product has been approved, a petition has been filed as provided by paragraph (f) of this section, and paragraph (e) of this section has been amended to specify the use as essential.

(e) The adulteration and misbranding provisions of paragraph (c) of this section shall not apply to the following essential uses of chlorofluorocarbons:

(1) Metered-dose steriod human drugs for nasal inhalation,

(2) Metered-dose steriod human drugs for oral inhalation,

(3) Metered-dose adrenergic bronchodilator human drugs for oral inhalation,

(4) Contraceptive vaginal foams for human use, and

(5) Metered-dose ergotamine tartrate drug products administered by oral inhalation for use in humans.

(6) Intrarectal hydrocortisone acetate for human use.

(7) Polymyxin B sulfate-bacitracin zinc-neomycin sulfate soluble antibiotic powder without excipients, for topical use on humans.

(8) Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application.

(9) Metered-dose nitroglycerin human drugs administered to the oral cavity.

(10) Metered-dose cromolyn sodium human drugs administered by oral inhalation.

(11) Metered-dose ipratropium bromide for oral inhalation.

(12) Metered-dose atropine sulfate aerosol human drugs administered by oral inhalation.

(13) Metered-dose nedocromil sodium human drugs administered by oral inhalation.

(14) Metered-dosed ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use.

(15) Sterile aerosol talc administered intrapleurally by thoracoscopy for human use.

(f) Any person may file a petition in accordance with part 10 of this chapter to amend paragraph (e) of this section to specify a use of chlorofluorocarbons in a product as not being subject to the adulteration and misbranding provisions in paragraph (c) of this section. The petition must be supported by an adequate showing that:

(1) There are no technically feasible alternatives to the use of a chlorofluorocarbon in the product,

(2) The product provides a substantial health benefit, environmental benefit, or other public benefit that would not be obtainable without the use of the chlorofluorocarbon, and

(3) The use does not involve a significant release of chlorofluorocarbons into the atmosphere or that the release is warranted in view of the consequence if the use were not permitted.

(g) Any holder of an approved new drug application or new animal drug application for a drug product containing a chlorofluorocarbon in a self-pressurized container, except those drug products listed in paragraph (e) of this section, shall submit to the Food and Drug

Administration on or before October 1, 1978, either a supplemental application providing for a revised formulation complying with the requirements of Sec. 314.70 or Sec. 514.8 of this chapter or a letter requesting that a new drug application or a new animal drug application for the drug product containing chlorofluorocarbon be withdrawn and that the right to a hearing on the withdrawal of the application is waived.

(h)(1) Each manufacturer of a drug product listed in paragraph (e) of this section that is not covered by an approved new drug application shall submit a new drug application in accord with Sec. 314.50 of this chapter on or before June 15, 1978.

(2) An abbreviated new drug application conforming to Sec. 314.94 of this chapter is acceptable in lieu of a full new drug application for any product included in the classes of products in paragraph (e) of this section if the product is one that is described under Sec. 314.92 of this chapter. A finding has been made that an abbreviated new drug application may be submitted for the following products included in the classes of products listed in paragraph (e) of this section:

(i) Ergotamine tartrate supplied in a metered-dose aerosol form suitable for oral inhalation for the treatment of migraine headaches. Each measured dose must deliver a dose of the active ingredient equivalent to that contained in the product that has been the subject of a separate finding that an abbreviated new drug application is suitable.

(ii) Isoproterenol hydrochloride supplied in a metered-dose aerosol form suitable for oral inhalation for use as an adrenergic bronchodilator. Each measured dose must deliver a dose of the active ingredient equivalent to that contained in the products that have been the subject of a separate finding that an abbreviated new drug application is suitable.

(iii) Epinephrine, epinephrine bitartrate, or epinephrine hydrochloride (racemic) in a metered-dose aerosol form suitable for oral inhalation for use as an adrenergic bronchodilator. Each measured dose must deliver a dose of the active ingredient equivalent to that specified in an OTC proposed or final monograph issued under the provisions of 21 CFR part 330.

(iv) Nonoxynol 9 in an aerosol foam suitable for vaginal administration as a contraceptive foam. The aerosol foam must contain 8 to 12.5 percent of nonoxynol 9.

(i) Any sponsor of an ``Investigational New Drug Application'' (IND) or ``Notice of Claimed Exemption for a New Animal Drug'' (INAD) for a drug product containing a chlorofluorocarbon shall:

(1) Amend the IND or INAD on or before December 15, 1978, to revise the formulation removing the chlorofluorocarbon.

(2) Submit the information required under paragraph (f) of this section to amend paragraph (e) of this section to show that the use of chlorofluorocarbon is essential, or

(3) Submit the information required under paragraph (j) of this section requesting that studies with the drug product containing a chlorofluorocarbon propellant be allowed to be performed.

(j) Any sponsor of an IND or INAD who wishes to initiate or continue a study beyond December 15, 1978 on a drug product containing a chlorofluorocarbon shall submit a petition in accordance with part 10 of this chapter requesting that studies be permitted to collect the data to show that the use of the chlorofluorocarbon is an essential use. The petitions must be supported by the following:

(1) A description of the drug product,

(2) An explanation why a chlorofluorocarbon propellant is used in the product rather than another propellant or another dosage form of the product, and

(3) The benefit that the investigational product is believed to have and that the sponsor hopes to demonstrate by the studies.

(k) The Commissioner will initiate action to withdraw approval of an application or terminate an IND or INAD notice in accordance with the applicable provisions of section 505 of the act and parts 312 and 314 of this chapter, or section 512 of the act and parts 511 and 514 of this chapter upon failure of a holder of an approved new drug application or approved new animal drug application or sponsor of an IND or INAD notice to comply with the applicable provisions of this section.

(l) Food, drug, device, or cosmetic products manufactured or packaged on or after December 15, 1978, and finished products initially introduced into interstate commerce on or after April 15, 1979, shall comply with this regulation.

[43 FR 11316, Mar. 17, 1978, as amended at 44 FR 3961, Jan. 19, 1979; 44
FR 30334, May 26, 1979; 45 FR 22902, April 4, 1980; 51 FR 4591, Feb. 6, 1986; 52 FR 15717, Apr. 30, 1987; 54 FR 9034, Mar. 3, 1989; 55 FR 39267,
Sept. 26, 1990; 57 FR 17980, Apr. 28, 1992; 58 FR 6088, Jan. 26, 1993; 61 FR 15700, Apr. 9, 1996; 61 FR 25392, May 21, 1996]

Note: **The following law pertains to drug products containing active ingredients offered over-the-counter (OTC) for human use as an anticholinergic in cough-cold drug products.**

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 310--NEW DRUGS--Table of Contents

Subpart E--Requirements for Specific New Drugs or Devices

Sec. 310.533 Drug products containing active ingredients offered over-the-counter (OTC) for human use as an anticholinergic in cough-cold drug products.

(a) Atropine sulfate, belladonna alkaloids, and belladonna alkaloids as contained in Atropa belladonna and Datura stramonium have been present as ingredients in cough-cold drug products for use as an anticholinergic. Anticholinergic drugs have been marketed OTC in cough-cold drug products to relieve excessive secretions of the nose and eyes, symptoms that are commonly associated with hay fever, allergy, rhinitis, and the common cold. Atropine sulfate for oral use as an anticholinergic is probably safe at dosages that have been used in marketed cough-cold products (0.2 to 0.3 milligram); however, there are

inadequate data to establish general recognition of the effectiveness of this ingredient. The belladonna alkaloids, which contain atropine (d, dl hyoscyamine) and scopolamine (l- hyoscine), are probably safe for oral use at dosages that have been used in marketed cough-cold products (0.2 milligram) but there are inadequate data to establish general recognition of the effectiveness of these ingredients as an anticholinergic for cough-cold use. Belladonna alkaloids for inhalation use, as contained in Atropa belladonna and Datura stramonium, are neither safe nor effective as an OTC anticholinergic. There are inadequate safety and effectiveness data to establish general recognition of the safety and/or effectiveness or any of these ingredients, or any other ingredient, for OTC use as an anticholinergic in cough-cold drug products.

(b) Any OTC cough-cold drug product that is labeled, represented, or promoted for use as an anticholinergic is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any cough-cold drug product labeled, represented, or promoted for OTC use as an anticholinergic is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After the effective date of the final regulation, any such OTC cough-cold drug product that is labeled, represented, or promoted for use as an anticholinergic may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application.

[50 FR 46587, Nov. 8, 1985, as amended at 55 FR 11579, Mar. 29, 1990]

Note: The following law pertains to drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. Due to the extensiveness of the list, the relevant portions have been excerpted with particular information to atropine highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 310--NEW DRUGS--Table of Contents

Subpart E--Requirements for Specific New Drugs or Devices

Sec. 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on

evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses:

(ii) Approved as of October 7, 1996.

Calcium sucrose phosphate
Dicalcium phosphate dihydrate
Disodium hydrogen phosphate

\1\ These ingredients are nonmonograph except when used to prepare acidulated phosphate fluoride treatment rinses identified in Sec. 355.10(a)(3) of this chapter.

Phosphoric acid[1]
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium phosphate, dibasic anhydrous reagent[1]

(3) Antidiarrheal drug products.

Aluminum hydroxide
Atropine sulfate
Calcium carbonate
Carboxymethylcellulose sodium
Glycine
Homatropine methylbromide
Hyoscyamine sulfate
Lactobacillus acidophilus
Lactobacillus bulgaricus
Opium, powdered
Opium tincture
Paregoric
Phenyl salicylate
Scopolamine hydrobromide
Zinc phenolsulfonate

(23) Internal analgesic drug products. (i) Approved as of November 10, 1993.

(ii) Approved as of February 22, 1999.

Any atropine ingredient
Any ephedrine ingredient

(24) Orally administered menstrual drug products. (i) Approved as of November 10, 1993.

(ii) Approved as of February 22, 1999.

Any atropine ingredient
Any ephedrine ingredient

(26) Anorectal druq products--(i) Anticholinergic drug products.

Atropine
Belladonna extract

Note: The following law pertains to the recommended warning and caution statements with respect to certain drugs. Due to the extensiveness of the list, the relevant portions have been excerpted with particular information to atropine highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 369--INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE--Table of Contents

Subpart B--Warning and Caution Statements for Drugs

Sec. 369.20 Drugs; recommended warning and caution statements.

BELLADONNA PREPARATIONS AND PREPARATIONS OF ITS ALKALOIDS (ATROPINE, HYOSCYAMINE, AND SCOPOLAMINE (HYOSCINE); HYOSCYAMUS, STRAMONIUM, THEIR DERIVATIVES, AND RELATED DRUG PREPARATIONS.

Warning--Not to be used by persons having glaucoma or excessive pressure within the eye, by elderly persons (where undiagnosed glaucoma or excessive pressure within the eye occurs most frequently), or by children under 6 years of age, unless directed by a physician. Discontinue use if blurring of vision, rapid pulse, or dizziness occurs. Do not exceed recommended dosage. Not for frequent or prolonged use. If dryness of the mouth occurs, decrease dosage. If eye pain occurs, discontinue use and see your physician immediately as this may indicate undiagnosed glaucoma.

In the case of scopolamine or scopolamine aminoxide preparations indicated for insomnia, the portion of the above warning that reads ``children under 6 years of age'' should read instead ``children under 12 years of age''.

Note: The following law pertains to the exemption from certain drug-labeling requirements. Relevant information has been italicized and highlighted.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 500--GENERAL--Table of Contents

Subpart C--Animal Drug Labeling Requirements

Sec. 500.55 Exemption from certain drug-labeling requirements.

(a) Section 201.105(c) of this chapter provides that in the case of certain drugs for which directions, hazards, warnings, and use information are commonly known to practitioners licensed by law, such information may be omitted from the dispensing package. Under this proviso, the Commissioner of Food and Drugs will offer an opinion, upon written request, stating reasonable grounds therefore on a proposal to omit such information from the dispensing package.

(b) The Commissioner of Food and Drugs has considered submitted material covering a number of drug products and has offered the opinion that the following drugs when intended for those veterinary uses for which they are now generally employed by the veterinary medical profession, should be exempt from the requirements of Sec. 201.105(c) of this chapter, provided that they meet the conditions prescribed in this paragraph. Preparations that are not in dosage unit form (for example, solutions) will be regarded as meeting the conditions with respect to the maximum quantity of drug per dosage unit if they are prepared in a manner that enables accurate and ready administration of a quantity of drug not in excess of the stated maximum per dosage unit:

Atropine sulfate. As an injectable for cattle, goats, horses, pigs, and sheep, not in excess of 15 milligrams per dosage unit; as an injectable for cats and dogs, not in excess of 0.6 milligram per dosage unit. Barbital sodium. For oral use in cats and dogs, not in excess of 300 milligrams per dosage unit.

Epinephrine injection. 1:1,000. For cats, dogs, cattle, goats, horses, pigs, and sheep (except as provided in Sec. 500.65).

Morphine sulfate. As an injectable for dogs, not in excess of 15 milligrams per dosage unit.

Pentobarbital sodium. For oral use in cats and dogs, not in excess of 100 milligrams per dosage unit.

Phenobarbital sodium. For oral use in cats and dogs, not in excess of 100 milligrams per dosage unit.

Procaine hydrochloride injection. Containing not in excess of 2 percent procaine hydrochloride, with or without epinephrine up to a concentration of 1:50,000. For use in cats, dogs, cattle, goats, horses, pigs, and sheep.

Thyroid. For oral use in dogs, not in excess of 60 milligrams per dosage unit.

Note: The following law pertains to Trichlorfon and Atropine.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 520--ORAL DOSAGE FORM NEW ANIMAL DRUGS--Table of Contents

Sec. 520.2520b Trichlorfon and atropine.

(a) Chemical name. (1) For trichlorfon: O,O-Dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate.

(2) For atropine: Atropine N.F.

(b) Sponsor. See No. 000856 in Sec. 510.600(c) of this chapter.

(c) Conditions of use. (1) The drug is used for the treatment of Syphacia obvelata (pinworm) in laboratory mice.

(2) It is administered in distilled water as sole source of drinking water continuously for 7 to 14 days at 1.67 grams of trichlorfon and 7.7 milligrams of atropine per liter.

(3) Prepare fresh solution every 3 days. Do not use simultaneously with other drugs, insecticides, pesticides, or chemicals having cholinesterase activity, nor within 7 days before or after treatment with any other cholinesterase inhibitor.

(4) Restricted to use by or on the order of a licensed veterinarian.

Note: The following law pertains to droperidol and fentanyl citrate injection. Relevant information directly related to atropine has been highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 522--IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS--Table of Contents

Sec. 522.800 Droperidol and fentanyl citrate injection.

(a) Specifications. Droperidol and fentanyl citrate injection is a sterile solution containing 20 milligrams of droperidol and 0.4 milligram of fentanyl citrate per cubic centimeter.

(b) Sponsor. See No. 000061 in Sec. 510.600(c) of this chapter.

(c) Conditions of use. (1) It is used in dogs as an analgesic and tranquilizer and for general anesthesia.

(2) It is administered as follows:

(i) For analgesia and tranquilization administer according to response desired, as follows:

(a) Intramuscularly at the rate of 1 cubic centimeter per 15 to 20 pounds of body weight ***in conjunction with atropine sulfate administered*** at the rate of 0.02 milligram per pound of body weight, or

(b) Intravenously at the rate of 1 cubic centimeter per 25 to 60 pounds of body weight ***in conjunction with atropine sulfate administered*** at the rate of 0.02 milligram per pound of body weight.

(ii) For general anesthesia administer according to response desired, as follows:

(a) Intramuscularly at the rate of 1 cubic centimeter per 40 pounds of body weight ***in conjunction with atropine sulfate administered*** at the rate of 0.02 milligram per pound of body weight and followed in 10 minutes by an intravenous administration of sodium pentobarbital at the rate of 3 milligrams per pound of body weight, or

(b) Intravenously at the rate of 1 cubic centimeter per 25 to 60 pounds of body weight ***in conjunction with atropine sulfate administered*** at the rate of 0.02 milligram per pound of body weight and followed within 15 seconds by an intravenous administration of sodium pentobarbital at the rate of 3 milligrams per pound of body weight.

(3) For use only by or on the order of a licensed veterinarian.

[40 FR 13858, Mar. 27, 1975, as amended at 64 FR 15684, Apr. 1, 1999]

Note: The following law pertains to sterile pralidoxime chloride. Relevant information related to atropine has been highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 522--IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS--Table of Contents

Sec. 522.1862 Sterile pralidoxime chloride.

(a) Chemical name. 2-Formyl-1-methylpyridinium chloride oxime.

(b) Specifications. Sterile pralidoxime chloride is packaged in vials. Each vial contains 1 gram of sterile pralidoxime chloride powder and includes directions for mixing this gram with 20 cubic centimeters of sterile water for injection prior to use.

(c) Sponsor. See No. 000856 in Sec. 510.600(c) of this chapter.

(d) Conditions of use. (1) It is used in horses, dogs, and cats as an antidote in the treatment of poisoning due to those pesticides and chemicals of the organophosphate class which have anticholinesterase activity in horses, dogs, and cats.

(2) It is administered as soon as possible after exposure to the poison. Before administration of the sterile pralidoxime chloride, atropine is administered intravenously at a dosage rate of 0.05 milligram per pound of body weight, followed by administration of an additional 0.15 milligram of atropine per pound of body weight administered intramuscularly. Then the appropriate dosage of sterile pralidoxime chloride is administered slowly intravenously. The dosage rate for sterile pralidoxime chloride when administered to horses is 2 grams per horse. When administered to dogs and cats, it is 25 milligrams per pound of body weight. For small dogs and cats, sterile pralidoxime chloride may be administered either intraperitoneally or intramuscularly. A mild degree of atropinization should be maintained for at least 48 hours. Following severe poisoning, a second dose of

sterile pralidoxime chloride may be given after 1 hour if muscle weakness has not been relieved.

(3) For use only by or on the order of a licensed veterinarian.

[40 FR 13858, Mar. 27, 1975, as amended at 49 FR 32061, Aug. 10, 1984]

Note: The following law pertains to dichlorvos. Relevant information relating to atropine has been highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 558--NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS--Table of Contents

Subpart B--Specific New Animal Drugs for Use in Animal Feeds

Sec. 558.205 Dichlorvos.

(a) Approvals. Type A medicated articles: 3.1 and 9.6 percent to 000010 in Sec. 510.600(c) of this chapter.

(b) Special considerations. (1) Dichlorvos is to be included in meal or mash or mixed with feed in crumble form only after the crumble feed has been manufactured. Do not mix in feeds to be pelleted nor with pelleted feed. Do not soak the feed or administer as wet mash. Feed must be dry when administered. Do not use in animals other than swine. Do not allow fowl access to feed containing this preparation or to feces from treated animals.

(2) ***Dichlorvos is a cholinesterase inhibitor. Do not use this product in animals simultaneously or within a few days before or after treatment with or exposure to cholinesterase-inhibiting drugs, pesticides, or chemicals. If human or animal poisoning should occur, immediately consult a physician or a veterinarian. Atropine is antidotal.***

(3) Labeling for Type A articles and Type B feeds must include a statement that containers or materials used in packaging such Type A articles and Type B feeds are not to be reused and all such packaging materials must be destroyed after the product has been used.

(c) Related tolerances. See Sec. 556.180 of this chapter.

(d) Conditions of use. It is used in feed for swine as follows:

(1) Amount per ton. Dichlorvos, 348 grams (0.0384 percent).

(i) Indications for use. For the removal and control of mature, immature, and/or fourth-stage larvae of the whipworm (Trichuris suis), nodular worm (Oesophagostomum sp.), large roundworm (Ascaris suum) and the thick stomach worm (Ascarops strongylina) of the gastrointestinal tract.

(ii) Limitations. For swine up to 70 pounds body weight, feed as sole ration for 2 consecutive days. For swine from 70 pounds to market weight, feed as sole ration at the rate of 8.4 pounds of feed per head until the medicated feed has been consumed. For boars, open or bred

gilts, and sows, feed as sole ration at the rate of 4.2 pounds per head per day for 2 consecutive days.

(2) Amount per ton. Dichlorvos, 479 grams (0.0528 percent).

(i) Indications for use. For the removal and control of mature, immature, and/or fourth-stage larvae of the whipworm (Trichuris suis), nodular worm (Oesophagostomum sp.), large roundworm (Ascaris suum), and the thick stomach worm (Ascarops strongylina) of the gastrointestinal tract.

(ii) Limitations. For boars, open or bred gilts, and sows, feed as sole ration at the rate of 6 pounds per head for one feeding.

(3) Amount per ton. Dichlorvos, 334-500 grams (0.0366-0.0550 percent).

(i) Indications for use. An aid in improving litter production efficiency by increasing pigs born alive, birth weights, survival to market, and rate of weight gain. Treatment also removes and controls mature, immature and/or fourth stage larvae of whipworm (Trichuris suis), nodular worm (Oesophagostomum supp.) large roundworm (Ascaris suum), and the thick stomach worm (Ascarops strongylina) occurring in the gastrointestinal tract of the sow or gilt.

(ii) Limitations. For pregnant swine; mix into a gestation feed to provide 1,000 milligrams per head daily during last 30 days of gestation.

[40 FR 13959, Mar. 27, 1975, as amended at 40 FR 50258, Oct. 29, 1975; 48 FR 46515, Oct. 13, 1983; 51 FR 7397, Mar. 3, 1986; 51 FR 28547, Aug. 8, 1986; 52 FR 2684, Jan. 26, 1987; 62 FR 35077, June 30, 1997]

Note: The following law is Schedule IV of Controlled Substances. Relevant information regarding atropine has been highlighted and italicized.

TITLE 21-FOOD AND DRUGS

CHAPTER II--DRUG ENFORCEMENT ADMINISTRATION, DEPARTMENT OF JUSTICE

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES--Table of Contents

Sec. 1308.14 Schedule IV.

(a) Schedule IV shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. Each drug or substance has been assigned the DEA Controlled Substances Code Number set forth opposite it.

(b) Narcotic drugs. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below:

(1) Not more than 1 milligram of difenoxin and not less than 25 9167 micrograms of atropine sulfate per dosage unit.....

(2) Dextropropoxyphene (alpha-(+)-4-dimethylamino-1,2-diphenyl-3- 9278
methyl-2-propionoxybutane).....

(c) Depressants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Alprazolam..... 2882
(2) Barbital..... 2145
(3) Bromazepam..... 2748
(4) Camazepam..... 2749
(5) Chloral betaine..... 2460
(6) Chloral hydrate..... 2465
(7) Chlordiazepoxide..... 2744
(8) Clobazam..... 2751
(9) Clonazepam..... 2737
(10) Clorazepate..... 2768
(11) Clotiazepam..... 2752
(12) Cloxazolam..... 2753
(13) Delorazepam..... 2754
(14) Diazepam..... 2765
(15) Dichloralphenazone..... 2467
(16) Estazolam..... 2756
(17) Ethchlorvynol..... 2540
(18) Ethinamate..... 2545
(19) Ethyl loflazepate..... 2758
(20) Fludiazepam..... 2759
(21) Flunitrazepam..... 2763
(22) Flurazepam..... 2767
(23) Halazepam..... 2762
(24) Haloxazolam..... 2771
(25) Ketazolam..... 2772
(26) Loprazolam..... 2773
(27) Lorazepam..... 2885
(28) Lormetazepam..... 2774
(29) Mebutamate..... 2800
(30) Medazepam..... 2836
(31) Meprobamate..... 2820
(32) Methohexital..... 2264
(33) Methylphenobarbital (mephobarbital)..... 2250
(34) Midazolam..... 2884
(35) Nimetazepam..... 2837
(36) Nitrazepam..... 2834
(37) Nordiazepam..... 2838
(38) Oxazepam..... 2835
(39) Oxazolam..... 2839
(40) Paraldehyde..... 2585
(41) Petrichloral..... 2591
(42) Phenobarbital..... 2285
(43) Pinazepam..... 2883
(44) Prazepam..... 2764
(45) Quazepam..... 2881
(46) Temazepam..... 2925

(47) Tetrazepam..... 2886
(48) Triazolam..... 2887
(49) Zaleplon..... 2781
(50) Zolpidem..... 2783

(d) Fenfluramine. Any material, compound, mixture, or preparation which contains any quantity of the following substances, including its salts, isomers (whether optical, position, or geometric), and salts of such isomers, whenever the existence of such salts, isomers, and salts of isomers is possible:

(1) Fenfluramine..... 1670

(e) Stimulants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system, including its salts, isomers and salts of isomers:

(1) Cathine ((+)-norpseudoephedrine)..... 1230
(2) Diethylpropion..... 1610
(3) Fencamfamin..... 1760
(4) Fenproporex..... 1575
(5) Mazindol..... 1605
(6) Mefenorex..... 1580
(7)Modafinil..... 1680
(8) Pemoline (including organometallic complexes and chelates 1530
thereof).....
(9) Phentermine..... 1640
(10) Pipradrol..... 1750
(11) Sibutramine..... 1675
(12) SPA ((-)-1-dimethylamino- 1,2-diphenylethane)..... 1635

(f) Other substances. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture or preparation which contains any quantity of the following substances, including its salts:

(1) Pentazocine..... 9709
(2) Butorphanol (including its optical isomers)..... 9720

[39 FR 22143, June 20, 1974]

Editorial Note: For Federal Register citations affecting Sec. 1308.14, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and on GPO Access.

Note: The following law is Schedule V of Controlled Substances. Relevant information regarding atropine has been highlighted and italicized.

TITLE 21-FOOD AND DRUGS

CHAPTER II--DRUG ENFORCEMENT ADMINISTRATION, DEPARTMENT OF JUSTICE

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES--Table of Contents

Sec. 1308.15 Schedule V.

(a) Schedule V shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section.

(b) Narcotic drugs. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation containing any of the following narcotic drugs and their salts, as set forth below:

(1) Buprenorphine..... 9064

(c) Narcotic drugs containing non-narcotic active medicinal ingredients. Any compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below, which shall include one or more non-narcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by narcotic drugs alone:

(1) Not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.

(2) Not more than 100 milligrams of dihydrocodeine per 100 milliliters or per 100 grams.

(3) Not more than 100 milligrams of ethylmorphine per 100 milliliters or per 100 grams.

(4) Not more than 2.5 milligrams of diphenoxylate and not less than 25 micrograms of atropine sulfate per dosage unit.

(5) Not more than 100 milligrams of opium per 100 milliliters or per 100 grams.

(6) Not more than 0.5 milligram of difenoxin and not less than 25 micrograms of atropine sulfate per dosage unit.

(d) Stimulants. Unless specifically exempted or excluded or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system, including its salts, isomers and salts of isomers:

(1)
Pyrovalerone.....1485.
(2) [Reserved]

[39 FR 22143, June 20, 1974, as amended at 43 FR 38383, Aug. 28, 1978; 44 FR 40888, July 13, 1979; 47 FR 49841, Nov. 3, 1982; 50 FR 8108, Feb. 28, 1985; 52 FR 5952, Feb. 27, 1987; 53 FR 10870, Apr. 4, 1988; 56 FR

61372, Dec. 3, 1991]

Excluded Nonnarcotic Substances

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[32]

Regulatory: EPA/NIEHS/Other Sources
EPA:

Note: The following is excerpted from a Safety Healthcare Handbook issued by the EPA regarding Biologicals and Insecticides of Biological Origin.

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5. Atropine sulfate. There is no specific antidote for nicotine poisoning. Severe hypersecretion (especially salivation and diarrhea) or bradycardia may be treated with intravenous atropine sulfate. See dosage on next page.
Dosage of Atropine Sulfate:
• *Adults and children over 12 years:* 0.4-0.5 mg slowly IV, repeated every 5 minutes if necessary.
• *Children under 12 years:* 0.01 mg/kg body weight, slowly IV, repeated every 5 minutes if necessary. There is a minimum dose of 0.1 mg.
6. Convulsions should be controlled as outlined in Chapter 2. If the patient survives for four hours, complete recovery is likely.[33]

Note: The following is a study presented by the EPA regarding the neurotoxicity of disulfoton in hens. The study was conducted alongside the use of atropine as well, hence its relevance to this report.

EXECUTIVE SUMMARY: In an acute delayed neurotoxicity study in hens (MRID# 44996401), disulfoton was acutely administered orally to 18 LSL laying hens at 40 mg/kg bird in a single dose. Fifteen hens were used as controls. Doses were administered in aqueous 2% Cremophor at 5 ml/kg bird. Five to 18 minutes before administration of the disulfoton, atropine was administered s.c. (0.5 ml/kg of 4% atropine sulfate). Directly prior to the administration of the disulfoton, 0.5 ml/kg of 10% atropine sulfate and 10% 2-PAM chloride was injected s.c. The afternoon of day 0, 0.5 ml/kg of 5% atropine sulfate and 5% 2-PAM chloride was injected s.c. and again the morning and afternoon of day 1. Clinical observations were made at least daily.

Forced motor activity tests were conducted by forcing the hens to run around a 12-13 m area and rated for coordination, ataxia, and paresis. NTE studies were conducted at 24 and 48 hours on the spinal cords, sciatic nerves and ½ of the brain in each of 3 hens per group. Cholinesterase activity studies were conducted on the other ½ of the brain from each bird in the NTE study at 24

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[32] All above laws regarding epinephrine and its legal use were directly copied and pasted from the government archives found on the web under relevant sections that pertained to this research. No alterations were made except certain significant information within the original text was highlighted for convenience purposes as previously noted. http://www.accessdata.fda.gov/scripts
[33] *Biologicals and Insecticides of Biological Origin.* http://www.epa.gov/pesticides/safety/healthcare/handbook/Chap07.pdf

and 48 hours post treatment. The study was conducted at 1.4 times the LD50 for hens. No typical signs of organophosphate induced delayed neuropathy was seen during the study or on microscopic examination of the treated birds at termination at 3 weeks. No inhibition was seen in the NTE study at 24 hours or 48 hours. Inhibition was low between 4% and 8% and was not considered to be indicative of OPIDP. Cholinesterase activity in the brain was inhibited 83% and 59% at 24 and 48 hours, respectively. No hens died, but by day 7 there was a decrease in body weight of over 5%. The hens slowly recovered and by the end of 3 weeks, body weight of the treatment group and of the controls did not differ.

Severely uncoordinated gait was observed in all treated birds within 5 minutes of being dosed with atropine and before disulfoton treatment. ***The report authors attributed this abnormal gait to atropine since it lasted only for the duration of the atropine treatment (2 days). However, the report authors also noted reduced motility in 1-3 birds for 0-1 day, which they attributed to disulfoton treatment. Neither statement is completely supportable because the hens were dosed with atropine and disulfoton during most of this period.*** However, the temporary uncoordinated gait was followed by no microscopic findings in nerve tissue and no other signs, which supports a conclusion of no demonstrated OPIDP in hens dosed with disulfoton.

Microscopic examination of the test birds showed 3 (25% - 8% in each region, grade 1) lesions in treated birds and 1 (11%, grade 1) in the same control brain regions. Since these lesions were similar to those found in controls from previous studies, they were considered incidental.

The study supports a conclusion the disulfoton does not cause acute delayed neuropathy (OPIDP) in hens.

The study is acceptable for an acute delayed neurotoxicity study (OPPTS# 870.6100) in hens.[34]

OSHA: none
IARC: not listed as a known carcinogen
NTP: not listed as a known carcinogen
NIEHS:

Note: The following is an excerpt from the Material Safety Data Sheet regarding clorpyrifos.

FOR CHOLINESTERASE INHIBITORS: Establish clear airway and tissue oxygenation by aspiration of secretions, and if necessary, by assisted pulmonary ventilation with oxygen. Improve tissue oxygenation as much as possible before administering atropine to minimize the risk of ventricular fibrillation. Administer atropine sulfate intravenously, or intramuscularly if iv injection is not possible. In moderately severe poisoning administer atropine sulfate, 0.4-2.0 mg repeated every 15 minutes until atropinization is achieved (tachycardia, flushing, dry mouth, mydriasis). Maintain atropinization by repeated doses for 2-12 hours, or longer, depending on the severity of poisoning. The appearance of rales in the lung bases, miosis, salivation, nausea, bradycardia, are all indications of inadequate atropinization. Severely poisoned individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be needed. Persons not poisoned or only slightly poisoned, however, may develop signs of atropine toxicity from such large dosages: Fever, muscle fibrillations, and delirium are the main signs of atropine toxicity. If these signs appear while the patient is fully atropinized, atropine administration

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[34] United States Environmental Protection Agency: Office of Prevention, Pesticides and Toxic Substances. *Acute Delayed Neurotoxicity and NTE Studies in Hens with Disulfoton.* http://www.epa.gov/pesticides/op/disulfoton/hens.pdf

should be discontinued, at least temporarily. Observe treated patients closely at least 24 hours to insure that symptoms (possibly pulmonary edema) do not recur as atropinization wears off. In very severe poisonings, metabolic disposition of toxicant may require several hours or days during which atropinization must be maintained. Markedly lower levels of urinary metabolites indicate that atropine dosage can be tapered off. As dosage is reduced, check the lung bases frequently for rales. If rales are heard or other symptoms return, re-establish atropinization promptly (Morgan, Recognition and Management of Pesticide Poisonings, 3rd Ed.).Administration of antidote must be performed by qualified medical personnel. In cases of severe poisoning by organophosphate pesticides in which respiratory depression, muscle weakness and twitchings are severe, give pralidoxime (Protopam-Ayerst, 2-PAM), 1.0 gram intravenously at no more than 0.5 gram per minute. Dosage of pralidoxime may be repeated in 1-2 hours,then at 10-12 hour intervals if needed. In very severe poisonings, dosage rates may be doubled. Treatment with pralidoxime will be most effective if given within thirty-six hours after poisoning (Morgan, Recognition and Management of Pesticide Poisonings, 3rd Ed.). Antidote should be administered by qualified medical personnel.[35]

NOSB: Atropine material is scheduled to be petitioned in September of 2002.
- Category: Livestock
  Petitioned use of material: Antidote for Poisoning

Status Among U.S. Certifiers

NOFA: There is nothing directly stated regarding atropine or any other antidote – whether prohibited or allowed. If considered for its pre-anesthetic purposes, atropine might be regulated by the following ruling listed by NOFA:

"The following medications are allowed with a 5 day withholding:
- non-steroidal anti-flammatory (i.e. banamine)
- antihistamines (e.g. epinephrine, adrenaline)
- anesthetics"[36]

NOFA includes agreements for the states of Connecticut, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, and Vermont.

Pennsylvania: adheres to the OMRI rulings. Nothing in particular has been mentioned regarding atropine or antidotes in general.

International

Canadian General Standards: Canada possesses 3 standards of beef—natural beef, certified organic beef, and certified hormone-free beef[37] Atropine is not listed in the Permitted Substances List for Livestock Production released by the Canadian General Standards Board regarding Organic Agriculture. As an antidote, considered an antibiotic, it is not permitted under the organic standard:

7.4 Health

7.4.4 No products from livestock treated with synthetic antibiotics, parasitides, or other synthetic veterinary compounds not permitted in this standard, with the exception of vaccines, shall be labeled or marketed as certified organic, in accordance with this standard, until an interval of time that is at least

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[35] *Chlorpyrifos.* http://www.uky.edu/~holler/html/msds.html
[36] VOF Organic Meat & Egg Production – NOFA Vermont http://www.nofavt.org/sht02_stds7.cfm
[37] Canada Beef Export Federation February 2001 http://www.agric.gov.ab.ca/agdex/400/420_830-3.pdf

double the permitted federal withdrawal period allowed for such veterinary compounds has been exceeded for the treated animal.[38]

EU: approved in the United Kingdom for single dose use in cattle (0.03 to 0.06 mg/kg [0.01 to 0.03 mg/lb] of body weight), sheep (0.08 to 0.16 mg/kg [0.04 to 0.07 mg/lb]), and pigs (0.02 to 0.04 mg/kg [0.0009 to 0.02 mg/lb]), SC, IM, or IV, with a 3-day milk and 14-day meat WDT. When used as an antidote at multiple does up to 0.2 mg/kg (0.09 mg/lb), a 6-day milk and 28-day meat WDT is recommended if the veterinarian is satisfied that there are no toxic residues from poison. [39]

Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

1. *The potential of the substance for detrimental interactions with other materials used in organic farming systems.*

Interactions:

ALTHOUGH THERE ARE NO SERIOUS DRUG INTERACTIONS WITH **ATROPINE**, AGENTS WITH MILD TO MODERATE ANTIMUSCARINIC ACTIONS...MAY...INTENSIFY EFFECTS OF **ATROPINE**. ALUMINUM-CONTAINING ANTACIDS & MAGNESIUM TRISILICATE PROBABLY INTERFERE WITH ABSORPTION...
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975. 840]**PEER REVIEWED**

ACTION OF **ATROPINE** POTENTIATES & IS POTENTIATED BY OTHER ANTICHOLINERGICS, SYMPATHOMIMETICS, CHOLINOLYTICS, MUSCARINIC RECEPTOR ANTAGONISTS. ACTION OF **ATROPINE** ANTAGONIZES & IS ANTAGONIZED BY CHOLINERGIC AGENTS, ANTICHOLINESTERASES, MUSCARINIC RECEPTOR AGONISTS, PARASYMPATHOMIMETICS, SYMPATHOLYTICS.

ATROPINE MAY ANTAGONIZE CNS DEPRESSANT DRUGS & POTENTIATE CNS EXCITATORY DRUGS. MAY EITHER POTENTIATE OR ANTAGONIZE TRANQUILIZERS. [40]

2. *The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment.*

FATALITIES FROM **ATROPINE**...ARE RARE, BUT SOMETIMES OCCUR IN CHILDREN. OF ALL POTENT ALKALOIDS, **ATROPINE** HAS ONE OF WIDEST MARGINS OF SAFETY. FATAL DOSE... NOT KNOWN; 200-MG DOSE..USED THERAPEUTICALLY FOR MENTAL ILLNESS, &...1000 MG HAVE BEEN SURVIVED. IN CHILDREN, 10 MG OR LESS MAY BE LETHAL.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 522]**PEER REVIEWED**

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[38] Canadian General Standards Board: National Standard of Canada. *Organic Agriculture.* CAN/CGSB-32.310-99
[39] *Extralabel use of tranquilizers and general anesthetics* http://www.farad.org/vets/digest4.html
[40] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2

DRY MOUTH, BLURRED VISION, PHOTOPHOBIA, ANHIDROSIS, & CONSTIPATION ARE UNAVOIDABLE SIDE EFFECTS...
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975. 840]**PEER REVIEWED**

...CONTRAINDICATED IN PERSONS WHOSE INTRAOCULAR PRESSURE IS...ELEVATED...IN PRESENCE OF PROSTATIC HYPERTROPHY OR ORGANIC PYLORIC STENOSIS. ...USED CAUTIOUSLY IN PT WITH PROSTATISM, URINARY RETENTION, DIABETES, HYPERTHYROIDISM, TACHYCARDIA, IN ELDERLY PERSONS, & CHILDREN UNDER 6 YR OF AGE.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975. 840]**PEER REVIEWED**

ATROPINE IS OF NO VALUE IN DELAYED TYPE OF MUSHROOM POISONING DUE TO TOXINS OF A PHALLOIDES & CERTAIN OTHER SPECIES OF SAME GENUS.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 531]**PEER REVIEWED**

Maternal Medication usually Compatible with Breast-Feeding: **Atropine**: Reported Sign or Symptom in Infant or Effect on Lactation: None. /fromTable 6/
[Report of the American Academy of Pediatrics Committee on Drugs in Pediatrics 93 (1): 140 (1994)]**QC REVIEWED**

Absorption, Distribution & Excretion:

BELLADONNA ALKALOIDS ARE ABSORBED RAPIDLY FROM GI TRACT. ...ENTER CIRCULATION WHEN APPLIED...TO MUCOSAL SURFACES... ONLY LIMITED ABSORPTION...FROM EYE & INTACT SKIN. ... **ATROPINE** DISAPPEARS RAPIDLY FROM BLOOD & IS DISTRIBUTED THROUGHOUT...BODY. MOST IS EXCRETED IN URINE WITHIN...12 HR. ...TRACES...FOUND IN...MILK.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 521]**PEER REVIEWED**

...WHEN ADMIN TO MOTHER PASS RAPIDLY INTO FETAL BLOOD.
[The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975. 634]**PEER REVIEWED**

IN DOG, 27% OF SC DOSE OF (3)H-**ATROPINE** WAS EXCRETED IN 2-HR URINE MOSTLY UNCHANGED. 50%...WAS EXCRETED WITHIN 6-HR, & RENAL EXCRETION OF **ATROPINE** OCCURRED BY GLOMERULAR FILTRATION & TUBULAR SECRETION.
[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume 1: A Review of the Literature Published Between 1960 and 1969. London: The Chemical Society, 1970. 69]**PEER REVIEWED**

AFTER IM ADMIN OF RADIOACTIVELY LABELED **ATROPINE** TO MAN, DISAPPEARANCE OF RADIOACTIVITY FROM PLASMA WAS BIPHASIC, WITH...HALF-LIVES OF 2 HR & 13-28 HR... BETWEEN 77 & 94% OF TOTAL RADIOACTIVITY WAS EXCRETED IN URINE... CHROMATOGRAPHIC EVIDENCE SUGGESTED THAT RELATIVE PROPORTIONS OF METABOLITIES VARIED WITH TIME.
[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume

2: A Review of the Literature Published Between 1970 and 1971. London: The Chemical Society, 1972. 455]**PEER REVIEWED**

Biological Half-Life:

AFTER IM ADMIN OF RADIOACTIVELY LABELED **ATROPINE** TO MAN, DISAPPEARANCE OF RADIOACTIVITY FROM PLASMA WAS BIPHASIC, WITH...HALF-LIVES OF 2 HR & 13-28 HR...
[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume 2: A Review of the Literature Published Between 1970 and 1971. London: The Chemical Society, 1972. 455]**PEER REVIEWED**[41]

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*

Natural Pollution Sources:

FROM ATROPA BELLADONNA L, DATURA STRAMONIUM L, & OTHER SOLANACEAE.
[The Merck Index. 9th ed. Rahway, New Jersey: Merck & Co., Inc., 1976. 117]**PEER REVIEWED**

...**ATROPINE** HAS NOT BEEN SHOWN TO OCCUR IN NATURAL SOURCES AS ALKALOID; IT IS RACEMIC MIXT OF D- & L-**HYOSCYAMINE**...
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975. 839]**PEER REVIEWED**

...**ATROPINE** MOLECULE CONSISTS OF 2 COMPONENTS JOINED THROUGH ESTER LINKAGE...**ATROPINE**, AN ORG BASE, &...TROPIC ACID.
[Jones, L.M., et al. Veterinary Pharmacology & Therapeutics. 4th ed. Ames: Iowa State University Press, 1977. 156]**PEER REVIEWED**[42]

4. *The effects of the substance on human health.*

Clinical Effects:

SUMMARY OF EXPOSURE

- MAJOR EFFECTS - Include delirium, hallucinations, tachycardia, hypertension, altered mental status, mydriasis, peripheral vasodilation, coma, seizures, warm red skin, dry mouth, dry axilla, urinary retention, dilated pupils, and diminished bowel signs. Any or all of these signs may occur with overdose or adverse reaction involving an anticholinergic. Effects may be delayed and cyclical.
- RARE EFFECTS - Occasionally, life-threatening arrhythmias (including bradycardia), cardiogenic shock,

[41] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2
[42] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2

or cardiorespiratory arrest may occur with certain anticholinergic drugs.

- Central anticholinergic effects may occur with drugs that do not easily cross the blood-brain barrier such as glycopyrrolate, a quaternary amine.
- EYE PREPARATIONS - Symptoms and signs of anticholinergic poisoning may occur following oral ingestion or ocular instillation of as little as 4 to 5 drops (probably less in children) of ocular solutions containing 4% **atropine** or 0.25% scopolamine.
- Tricyclic antidepressant overdose can cause an anticholinergic clinical picture but is characterized by severe cardiovascular and neurologic toxicity. Refer to "ANTIDEPRESSANTS, TRICYCLIC" management for further information.

VITAL SIGNS

- Vital sign changes include tachycardia and hypertension. Both hyperthermia and hypothermia have been reported, but hyperthermia is more common.

HEENT

- Warm red skin, decreased sweating, dry oral mucous membranes, and widely dilated pupils are common.

CARDIOVASCULAR

- Tachycardia and hypertension are most common. Cutaneous vasodilation may occur. Life-threatening arrhythmias and cardiorespiratory arrest occur rarely.
- Hypotension has been reported following diphenidol overdose.

RESPIRATORY

- Respiratory depression, respiratory failure, and aspiration may occur in severe overdoses.

NEUROLOGIC

- Toxic psychosis (disorientation, delirium, hallucinations, and paranoia associated with anxiety, agitation, and hyperactivity) has been reported. Memory loss has also been noted as a toxic anticholinergic effect. Seizures, dystonic reactions, and dyskinesias may occur at recommended doses. Severe poisoning may produce coma, medullary paralysis, and death.

GASTROINTESTINAL

- Decreased gastric motility, diminished bowel sounds, esophageal atony and dilatation, colonic distention, and paralytic ileus may occur as a result of anticholinergic toxicity.

GENITOURINARY

- Urinary retention may occur.

DERMATOLOGIC

- Warm red skin with decreased sweating is common. Delayed hypersensitivity has also been reported.

MUSCULOSKELETAL

- Rhabdomyolysis may occur.

PSYCHIATRIC

- Toxic psychosis (disorientation, delirium, hallucinations, and paranoia associated with anxiety, agitation, and hyperactivity) has been reported.

IMMUNOLOGIC

- Anaphylaxis has been reported following the use of certain anticholinergic drugs.

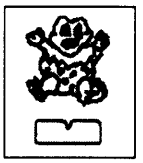
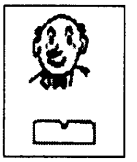
OTHER

- Anticholinergic drugs have an abuse potential because of their antidepressant and mood-elevating properties. In addition, a dependence and withdrawal syndrome has been associated with anticholinergic use.

[43]

DANGEROUS PILL WARNING

A campaign was started in the Netherlands by the Trimbos Institute warning for pills sold as xtc that contain atropine. This is a list of these pills and their details.

Diameter:	9 mm	9 mm	11 mm	9 mm	10 mm	10 mm	10 mm
Thickness:	3,4 mm	3,1 mm	3,6 mm	3,3 mm	3,4 mm	3,4 mm	3,4 mm
Colour:	White	White	white	Blue	white	white	white
Top:	Groove	Groove	groove	Groove	groove	groove	groove
Bottom:	SITTING TURTLE	DANCING TURTLE	ALIEN	DAGOBERT	LAMBIEK	MARIO	LUIGI
Logo:							
Side:							

What is ATROPINE? ATROPINE is a psychedelic causing hallucinations. This can make you very disturbed and confused (flipping). It only starts working after several hours and the effects can last for 24 hours. The dosage of the pills varies greatly, which can lead to overdosing. When you have taken one of the above pills, DO NOT TAKE another one of these pills or any other substance (legal or illegal drug)!

Atropine can seriously influence your vision and therefore your driving capabilities. Please be careful and try not to drive a car or other vehicle for four days after you have taken one of the above pills.

Some of you will state that the above pills have been around for a long time. This is correct but they did not contain atropine. Finally: the entire XTC market has been seriously polluted for several months now.

This message is brought to you by the *drugtext* foundation and the international harm reduction association with thanks to the *trimbos* institute, and gabbers on line.

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[43] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2

5. *The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.*

Non-Human Toxicity Excerpts:

MANY, BUT NOT ALL RABBITS...THRIVE ON BELLADONNA LEAVES, DUE TO HIGH LEVELS OF SERUM ATROPINESTERASE.
[Rossoff, I.S. Handbook of Veterinary Drugs. New York: Springer Publishing Company, 1974. 29]**PEER REVIEWED**

...**ATROPINE** HAD MARKEDLY GREATER TOXICITY IN NEONATES IN COMPARISON WITH ADULT EXPTL ANIMALS.
[The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975. 677]**PEER REVIEWED**

THERE IS...INTERSPECIES VARIATION IN TOXICITY OF...**ATROPINE**; ROUTE OF ADMIN IS ALSO IMPORTANT. ...CERTAIN STRAINS OF RABBITS...RESISTANT TO DIET... HOWEVER, RABBITS FED ON SUCH DIET MAY PROVE TOXIC IF EATEN BY DOGS, CATS... HORSES, CATTLE, & GOATS ARE...SUSCEPTIBLE TO **ATROPINE** WHEN IT IS INJECTED PARENTERALLY.
[Jones, L.M., et al. Veterinary Pharmacology & Therapeutics. 4th ed. Ames: Iowa State University Press, 1977. 158]**PEER REVIEWED**

SIGNS OF...POISONING ARE SIMILAR IN ALL MAMMALIAN SPECIES. DRY MOUTH, THIRST, DYSPHAGIA, CONSTIPATION, MYDRIASIS, TACHYCARDIA, HYPERPNEA, RESTLESSNESS, DELIRIUM, ATAXIA...MUSCLE TREMBLING...CONVULSIONS, RESP DEPRESSION, &...FAILURE LEAD TO DEATH.
[Jones, L.M., et al. Veterinary Pharmacology & Therapeutics. 4th ed. Ames: Iowa State University Press, 1977. 159]**PEER REVIEWED**

OVERDOSAGE MAY CAUSE PYREXIA...NERVOUSNESS...DEATH FROM RESP RATHER THAN CARDIAC FAILURE.
[Rossoff, I.S. Handbook of Veterinary Drugs. New York: Springer Publishing Company, 1974. 29]**PEER REVIEWED**

Metabolism/Metabolites:

...EXCRETED IN URINE...IN PART UNCHANGED, VARYING FROM 13-50%, & REMAINDER AS METABOLITE THAT HAS NOT YET BEEN DEFINITELY IDENTIFIED...
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 521]**PEER REVIEWED**

WITH (14)C RESTRICTED TO ALPHA-CARBON...ON TROPIC ACID PORTION...10 RADIOACTIVE...PRODUCTS...IN MOUSE & RAT URINE, PRINCIPAL METABOLITES WERE GLUCURONIDE CONJUGATES OF HYDROXYATROPINES FORMED IN VIVO BY METABOLIC HYDROXYLATION OF AROMATIC RING...GLUCURONIDES OF **ATROPINE** COULD NOT BE DETECTED IN HUMAN URINE...
[Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976.,p. III-44]**PEER REVIEWED**

ATROPINASE IS ENZYME IN BLOOD WHICH HYDROLYZES **ATROPINE**. IS VERY ACTIVE IN RABBIT BLOOD. **PEER REVIEWED**[44]

6. The alternatives to using the substance in terms of practices or other available materials.

Being that atropine is used as an antidote, there are not many alternatives. Atropine is used in cases of organophosphate poisoning and particularly for its cholinesterase blocking capabilities. As a result, there are no real substitutes for atropine.

Cholinesterase inhibitors act by poisoning acetylcholinesterase, which decomposes acetylcholine in the synapse and deactivates it. Cholinesterase is also distributed systemically in many tissues other than nerve synapses. Interestingly, a distinct enzyme called butyrylcholinesterase exists which is not inhibited by the usual organophosphate compounds. Anticholinergic agents block acetylcholine at its receptors. Other drugs called ganglion blockers or neuromuscular blockers directly block ion flow in the ion channel gated by the cholinergic receptor. Hexamethonium, for example, probably works mostly by ion channel blockade while trimethapan probably blocks the receptor but ot the channel. Tetraethylammonium is distinguished by having a very short duration of action. Mecamylamine, a secondary ammonium compound, is absorbed fairly well.

The atropine class of antimuscarinics blocks muscarinic receptors but are fairly inactive at nicotinic terminals. Atropine itself has been used as a war-gas antidote (see below). It is found in nature in the "deadly nightshade," Atropa belladonna and in jimsonweed (Datura stramonium), and is isomeric with hyoscamine. Scopolamine is a similar drug found in Hyoscamus niger (henbane). Benztropine, a synthetic variant, has been used against Parkinsonism.

Many of the drugs used by modern pharmacology are "incidentally" antimuscarinic, especially the phenothiazine (Thorazine) group of antipsychotic meds and the tricyclic (Elavil) group of antidepressants. Propantheline is an example of the former group, used as an antimuscarinic; pirenzepine of the latter. Pirenzepine appears to be selective for M1 receptors.[45]

7. Its compatibility with a system of sustainable agriculture.

With regards to a system of sustainable agriculture, there are many things that need to be considered: the animal's welfare, the environmental effects, as well as the overall effects in relation to human health. Atropine is a veterinarian controlled substance that is only administered when and if there is a poisoning of some sort. As a result, there are no real substitutes that will provide the same effect on the animal.

There are, however, some concerns with the drug as a whole. Although there is no real threat that it will dangerously combine with other substance, when it is disposed of through the animal's urine, after treatment, it comes out in nearly its original form. This has not been proven to cause any damage, but it is a long-run concern nonetheless.

As long as the withdrawal times and storage requirements are followed appropriately, there should not be any real threat to humans in general; at least when the concern is based on whether or not there will be detrimental remnants left in the beef products.

The most detrimental aspect of atropine is the plant it is derived from. Atropine is found with hyoscamine in the deadly nightshade plant *atropa belladonna.* It is this plant that is threatening to human health, but once again, atropine is merely *derived* from the plant and it does not necessarily contain its poisonous attributes in its individual makeup.

Atropine seems like it would be compatible with a system of sustainable agriculture but it is difficult to pass judgment without knowing ALL the facts. The extensive effects of the drug on the environment as a whole cannot be known for certain until time passes and the aftermath is noted, observed, and analyzed.

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[44] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2

[45] *Cholinergic Drugs.* http://www.pharmcentral.com/cholinergics.htm

TAP Reviewers' Discussion

Reviewer 1 *[Ph.D. Animal Nutrition, Post Doc. Nutritional Physiology. Professor, Animal Nutrition and Feeding. Southeast U.S]*

Observations/OFPA Criteria

The Organic Food Production Act of 1990 recognizes the need to administer medication in response to illness and requires producers to keep records of the amounts and sources of all medications administered (Sections 6509.d.1.C and 6509.f.2.A). The primary use of atropine in organic production of animals and animal products is as a medication administered by a licensed practitioner.

Circumstances requiring veterinary intervention and use of prescribed amounts of atropine appear to be limited to emergencies in which an animal's life is endangered. These include use of atropine as an antidote for organophosphate poisoning or as a pre-medication to reduce salivary and bronchial secretions during surgical procedures requiring general anesthesia. Because atropine is a specific, but transient, inhibitor of acetylcholine binding to muscarinic receptors in the parasympathetic nervous system, responses to prescribed doses are localized, rapid, and predictable. As such, atropine often used in combination with other drugs. An important practical example is the use of atropine in combination with protopam chloride to treat poisoning due to ingestion of cattle ear tags containing diazinon.

Atropine is rapidly cleared from the body, typically in less than 24 hours. The possibility of transferring atropine residues from a treated animal to food products consumed by humans is apparently minimal, but a withdrawal period should be established to assure the safety of children or those sensitive to small amounts of atropine. For organic food production, a suggested withdrawal period that is "at least double the permitted federal withdrawal period" seems prudent (page 31 in Atropine-Livestock). However, withdrawal period guidelines for milk (3 or 6 days) and meat (14 or 28 days) adopted by the European Union appear to exceed the above withdrawal period criteria for organic food products.

Reviewer 1 Conclusions

The primary uses of atropine are related to maintaining the health of animals in circumstances that could be viewed as medical emergencies. Therefore, restricted use of atropine, when indicated for treatment of animals under veterinary supervision, should be approved for use in organic food production.

Reviewer 1 Recommendations Advised to the NOSB

The substance is Synthetic.

For Livestock, the substance should be Added to the National List with restrictions.

Reviewer 2 *[Ph.D, Chemistry. Professor, Department of Chemistry. Southwest U.S.]*

Comments on Database

No additional information required.

Observations/OFPA Criteria

Atropine is a substance that can be derived from a plant. It can also be synthesized. However, I would define it as a natural substance.

It is used as an antidote for organophosphate poisoning. There are no viable alternatives. It is also used as a premedication for anesthesia.

There is doubt raised based on the fact that atropine is obtained from a poisonous plant. This in itself, however, does not mean that atropine is harmful to humans or to the environment. No significant data are provided to this end.

There is doubt raised on the grounds of being an "antibiotic." Atropine is not an antibiotic so this should not be an issue.

Reviewer 2 Conclusions

Given that atropine is a natural product with no obvious detrimental effects, I see no reason for it not to be allowed.

Reviewer 2 Recommendations Advised to the NOSB

The substance is Nonsynthetic.

For Livestock, the substance should be Added to the National List.

Reviewer 3 *[Ph.D. Animal Nutrition, Post Doc. Nutritional Physiology. Professor, Animal Nutrition and Feeding. Southeast U.S]*

Observations/OFPA Criteria

Itemization, Specific Use and Application

Atropine is used as an antidote to pesticide (organophosphate or carbamate) poisoning. It is derived from the plant *atropa belladonna.* It is not found in its natural alkaloid form alone, but is synthetically manufactured for commercial veterinary purposes.

Farmers are petitioning its use as the antidote for organophosphate poisoning. It is administered orally by a licensed veterinarian in cases where poisoning is suspected and is without a natural alternative.

Organic Foods Production Act: According to the final ruling by the OFPA, there is no real prohibition of atropine specifically stated although there are particular restraints for all antibiotics in general. There are no specific rulings against or in favor of antidotes in general. In order for atropine, a synthetic, to be used in organic production, it must be placed on the National List.

OFPA Section 2110:

(1) **Prohibited Practices**. For a farm to be certified under this chapter as an organic farm with respect to the livestock produced by such farm, producers on such farm shall not

(A) use subtherapeutic doses of antibiotics;

(B) use synthetic internal paraciticides on a routine basis; or

(C) administer medication, other than vaccinations, in the absence of illness. [46]

Potential Harm to Human Health or the Environment

The following is quoted from the scientific review. This information was not helpful to my review. Perhaps the NOSB will find it useful.

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[46] *6509 Animal Production Practices and Materials.* Federal Organic Food Production Act of 1990. http://www.ams.usda.gov/nop/orgact/htm

This reviewer's concern is about the pesticide poisoning and its impact on human health or the environment and on prevention of pesticide poisoning of organic animals. Putting a poisoned animal put back onto the organic market, after treatment with atropine is not consistent with the consumers' image of organic meat.

"Natural Pollution Sources:

FROM ATROPA BELLADONNA L, DATURA STRAMONIUM L, & OTHER SOLANACEAE.
[The Merck Index. 9th ed. Rahway, New Jersey: Merck & Co., Inc., 1976. 117]**PEER REVIEWED**

...**ATROPINE** HAS NOT BEEN SHOWN TO OCCUR IN NATURAL SOURCES AS ALKALOID; IT IS RACEMIC MIXT OF D- & L-**HYOSCYAMINE**...
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975. 839]**PEER REVIEWED**

...**ATROPINE** MOLECULE CONSISTS OF 2 COMPONENTS JOINED THROUGH ESTER LINKAGE...**ATROPINE**, AN ORG BASE, &...TROPIC ACID.
[Jones, L.M., et al. Veterinary Pharmacology & Therapeutics. 4th ed. Ames: Iowa State University Press, 1977. 156]**PEER REVIEWED**[47]"

Compatibility With A System of Sustainable Agriculture.

Since the NOP regulation requires the implementation of an organic system plan designed to keep organic product from contamination by a prohibited substance it is difficult to see how organic livestock would get pesticide poisoning. Methods should be in place on every organic farm to ensure that livestock does not have access to organophosphates as well as all other pesticides, whether or not they appear on the National List. Atropine is a veterinarian controlled substance that is only administered when and if there is a poisoning. It is the opinion of this reviewer that organic livestock, once poisoned by pesticides, should certainly be treated for the poisoning and then removed from the organic market.

The scientific review found some concerns with the drug "as a whole." "When it is disposed of through the animal's urine, after treatment, it comes out in nearly its original form. This has not been proven to cause any damage, but it is a long-run concern nonetheless. As long as the withdrawal times and storage requirements are followed appropriately, there should not be any real threat to humans in general; at least when the concern is based on whether or not there will be detrimental remnants left in the beef products."

This does not address, however, the affect of the pesticide on the beef, and any residues that may be left in the meat. Since atropine crosses into the fetus and into milk, it would not be suitable for use in dairy animals.

The reviewer also notes that: "Atropine seems like it would be compatible with a system of sustainable agriculture but it is difficult to pass judgment without knowing ALL the facts. The extensive effects of the drug on the environment as a whole cannot be known for certain until time passes and the aftermath is noted, observed, and analyzed."

"BELLADONNA ALKALOIDS ARE ABSORBED RAPIDLY FROM GI TRACT. ...ENTER CIRCULATION WHEN APPLIED...TO MUCOSAL SURFACES... ONLY LIMITED ABSORPTION...FROM EYE & INTACT SKIN. ... **ATROPINE** DISAPPEARS RAPIDLY FROM

[47] *HSDB Full Record* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAHOaGJG:2

BLOOD & IS DISTRIBUTED THROUGHOUT...BODY. MOST IS EXCRETED IN URINE WITHIN...12 HR. ...TRACES...FOUND IN...MILK.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 521]**PEER REVIEWED**

...WHEN ADMIN TO MOTHER PASS RAPIDLY INTO FETAL BLOOD.
[The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975. 634]**PEER REVIEWED**"

"Metabolism/Metabolites:
...EXCRETED IN URINE...IN PART UNCHANGED, VARYING FROM 13-50%, & REMAINDER AS METABOLITE THAT HAS NOT YET BEEN DEFINITELY IDENTIFIED...
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975. 521]**PEER REVIEWED**"

Consistent With Organic Farming?

Atropine is synthetically obtained and is used primarily in cattle that are suffering from Organophosphate poisoning. Administered by a licensed practitioner, atropine is generally given orally.

The use of Atropine is inconsistent with current Organic Farming practices in the US and Canada.

Status Among U.S. Certifiers
NOFA: There is nothing directly stated regarding atropine or any other antidote – whether prohibited or allowed.

International
Canadian General Standards: Canada possesses 3 standards of beef—natural beef, certified organic beef, and certified hormone-free beef[48] Atropine is not listed in the Permitted Substances List for Livestock Production released by the Canadian General Standards Board regarding Organic Agriculture.

EU: approved in the United Kingdom for single dose use in cattle (0.03 to 0.06 mg/kg [0.01 to 0.03 mg/lb] of body weight), sheep (0.08 to 0.16 mg/kg [0.04 to 0.07 mg/lb]), and pigs (0.02 to 0.04 mg/kg [0.0009 to 0.02 mg/lb]), SC, IM, or IV, with a 3-day milk and 14-day meat WDT. When used as an antidote at multiple does up to 0.2 mg/kg (0.09 mg/lb), a 6-day milk and 28-day meat WDT is recommended if the veterinarian is satisfied that there are no toxic residues from poison. [49]

Reviewer 3 Conclusions

Atropine is not necessary unless an animal has already ingested a substance prohibited for use in organic agriculture. At that time the organic integrity of the animal has already been destroyed.

Reviewer 3 Recommendations Advised to the NOSB

Atropine, the substance is a synthetic drug that is not *required* for the sustainability of an organic beef animal.

It should be Prohibitted and not allowed with OR without restrictions.

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[48]Canada Beef Export Federation February 2001 http://www.agric.gov.ab.ca/agdex/400/420_830-3.pdf
[49]*Extralabel use of tranquilizers and general anesthetics* http://www.farad.org/vets/digest4.html

TAP Conclusion

The three TAP reviewers are not all in agreement for the uses and restrictions of atropine and its overall inclusion into the NOSB list. Two of the reviewers agree that the substance is synthetic while one has claimed it to be nonsynthetic because of its derivation from a naturally occurring plant. One reviewer believes that the substance should be *allowed without restrictions*, one believes that it should be *allowed with restrictions*, and one says that the substance should be *completely prohibited not, no to be allowed with or without restrictions.* Those in agreement that atropine should be added to the NOSB list state that since it is an emergency drug administered only by a physician, it should be allowed. On the other hand, one of the reviewers believes that since the drug is only used in cases of severe pesticide poisoning, then the animal's organic requirements have already been compromised. Hence, the drug is not necessary. Based on the three different perspectives regarding the same drug, the final debate on whether or not atropine should be added to the NOSB list proves inconclusive.