BUTORPHANOL
Livestock

Executive Summary

Butorphanol is a synthetic drug more commonly made into butorphanol tartrate, which is the primary component of Torbugesic® (the injectable butorphanol tartrate solution). It has been FDA approved and used as an anesthetic in all types of animals over the past years. Administered intravenously, butorphanol is quickly broken down internally and cleared from the bloodstream in urine.

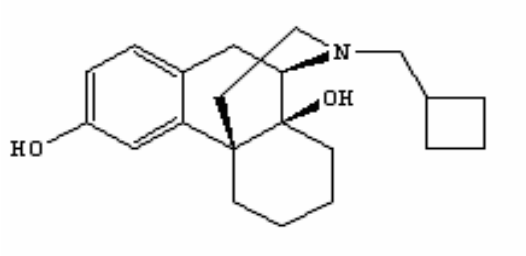
Organic farmers have petitioned the use of butorphanol for cattle in order to ease them prior to surgery under veterinary care. They would like to treat livestock in the need of surgery with butorphanol in order to help the animal deal with severe pain. If all precautions are followed and the drug is administered appropriately, there will be no harm done to humans who consume the meats from these animals—and the livestock are able to tolerate surgery, recover quickly, and grant the farmer economic satisfaction.

Summary of TAP Reviewers' Analyses[1]

Synthetic/ Nonsynthetic	***Allow without restrictions?***	***Allow only with restrictions? (See Reviewers' comments for restrictions)***
Yes (3)	Yes (1) No (2)	Yes (2)

Identification

Chemical names: Butorphanol, $C_{21}H_{29}NO_2$



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Other Names: (-)-17-(Cyclobutylmethyl)morphinan-3,14-diol; Butorfanol; Butorfanol [INN-Spanish]; Butorphanol; Butorphanolum [INN-Latin]; Morphinan-3,14-diol, 17-(cyclobutylmethyl)-; (S-(R*,R*))-2,3-dihydroxybutanedioate(1:1)(salt);

[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.*

Drug Names: Stadol®, Torate, Torbutrol®, Torbugesic®

CAS Number: 402408-82-2
Other Codes: EINECS 255-808-8
1-BC 2627
levo-1-BC 2627
DEA No. 9720
DEA Schedule IV[3]

Characterization

Composition:
Butorphanol is a synthetic narcotic used for surgical procedures. It is an opiate and an agonist-antagonist analgesic used help the animal deal with pain during surgery. As an administered drug, butorphanol exists as butorphanol tartrate and the injection form, whether Stadol®, used for humans, or Torbugesic® used for animals is compromised of the following:

Component	% By Weight	CAS #
Butorphanol Tartrate, USP	0.1-0.2%	58786-99-5
Sodium Chloride, USP	0.64%	7647-14-5
Sodium Citrate, USP	0.73%	68-04-2
Citric Acid, anhydrous USP	0.33%	77-92-9
Water for Injection USP	98.2-98.1%	7732-18-5

Butorphanol Tartrate Injection is a sterile injectable liquid drug provided in a vial.[4]

Properties:
Note: The following properties listed pertain to butorphanol tartrate, ingredient found in Torbugesic®;
Physical State: Liquid
Appearance: Clear, colorless
Odor: Odorless
Boiling Point: Approximate to water
Vapor Pressure: Approximate to water
Vapor Density: Approximate to water
pH: 7.5
Specific Gravity: Unknown
Melting Point: Not Applicable
Evaporation Rate: Unknown
Solubility in Water: Solution will mix well with water
Stability: Stable
Incompatibility: Strong oxidizers and water reactive materials
Hazardous Decomposition or Byproducts: As with many burning material, carbon monoxide, carbon dioxide, nitrogen oxides, and sulfur oxides may be produced.
Hazardous Polymerization: Will not occur
Conditions to Avoid: Storage with oxidizers and water reactive materials.[5]

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[2] http://www.utexas.edu/pharmacy/courses/phr452d/spr00.htm
[3] *Butorphanol [USAN:BAN:INN] RN: 42408-82-2.*
http://chem.sis.nlm.nih.gov/chemidplus/detail_frame.html?DetailIndex=1&DetailCount=5

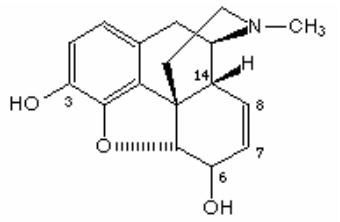
[4] *Material Safety Data Sheet*. Bedford Laboratories.
http://216.239.37.100/search?q=cache:NphtFBAwZG0C:www.bedfordlabs.com/msds/Butorph%2520Preserv.pdf+butorphanol+AND+melting+point&hl=en&ie=UTF8

How Made:

First appearing on the market as an injectable in 1979[6], butorphanol is an opioid analgesic derived from morphine. Known for the ability to reduce the perception of pain without a loss of consciousness, the original opioids were derived from opium, which is a partially dried latex harvested from the opium poppy, Papaver somniferum. Opium contains morphine, codeine, noscapine, papaverine, and thebaine. Thebaine is a convulsant drug that produces no analgesia, and as such it is not used clinically. However, it is an important synthetic intermediate in the production of semi-synthetic opioids. Opium is a less effective analgesic than pure morphine, because it is slowly absorbed, and has been historically used for its constipating action (paregoric). Morphine itself, which was discovered in 1809, has a variety of effects: an increase in the tolerance to pain, somnolence, euphoria, an antitussive effect, respiratory depression, constipation, and emesis. Morphine also has a high addiction liability. Derivatives of morphine, such as butorphanol, have been researched for their ability to retain the analgesic activity of the parent, but have improved the oral bioavailability while reducing the addiction liability and other deleterious side effects.

Note: The following is a lengthy discussion of morphine and its many derivatives. The paragraph relevant in particular to the construction butorphanol has been *italicized* and butorphanol, itself, boxed.

Morphine possesses an aromatic ring, a cyclohexane ring, a cyclohexene ring, poperidine, and tetrahydrofuran, as seen in the structure below. All of the derivatives of morphine which possess this basic ring structure have a high addiction liability which is proportional to their analgesic activity.



Morphine

Modifications at the 3- and 6-hydroxyl groups:

Conversion of the 3-OH to a 3-OCH3, yielding codeine, reduces activity to 15% of morphine. Groups larger than a methoxy reduce activity dramatically.

Conversion of the 6-OH to a 6-OCH3 yields heterocodeine, resulting in an increase in activity (six-fold).

Oxidation of the 6-OH to a ketone reduces activity when the 7,8-double bond is present (morphinone = 37% of morphine). However, as shown below, when the 7,8-double bond is saturated, a 6-keto will increase activity.

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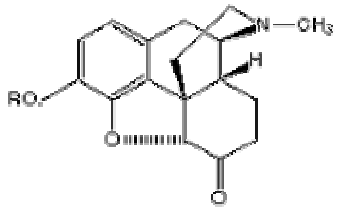
[5] *Material Safety Data Sheet*. Bedford Laboratories. http://216.239.37.100/search?q=cache:NphtFBAwZG0C:www.bedfordlabs.com/msds/Butorph%2520Preserv.pdf+butorphanol+AND+melting+point&hl=en&ie=UTF8

[6] *Drug Enforcement Administration Places Butorphanol into Schedule IV*. http://www.labanimal.com/col/reg1097.htm

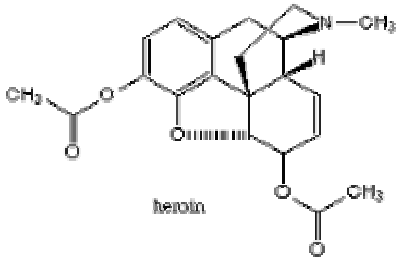


R = H, dihydromorphinone (6X as potent as dihydromorphine)
R = CH_3, dihydrocodeinone (4X as potent as dihydrocodeine)

Removal of the 6-OH (**6-desoxymorphine**) increases activity 10-fold in the dihydro series.

Acetylation of both the 3- and 6-OH produces 3,6-diacetylmorphine, also known as **heroin** . Heroin is 2-3 times more potent than morphine. Most of this increase is due to increased lipid solubility, which leads to enhanced and rapid CNS penetration.

If the ether linkage is opened up to afford a second OH on the aromatic ring, activity is reduced 90% (see below).



heroin

Modifications at the 7,8-double bond:

Reduction of the 7,8-double bond results in a slight increase in activity, as in dihydromorphine and dihydrocodeine.

As mentioned above, saturation of the 7,8-double bond has the greatest effect when combined with modifications at the 6-position (as in dihydromorphinone).

Modifications of the nitrogen substituent:

Methyl is the optimal substituent for agonist activity, and ethyl is passable.

If the nitrogen substituent is a hydrogen, analgesic effect is reduced 75%, and addicition liability is lowered.

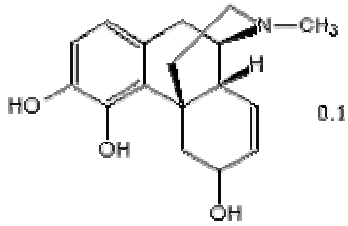
Addition of a phenethyl substituent in place of methyl results in a 14-fold increase in activity over morphine.

Quaternary ammonium derivatives such as N,N-dimethylmorphine have no analgesic activity, but do have significant curare-like activity.

If the nitrogen substituent is a bulky alkyl group such as propyl, isobutyl, or especially allyl and cyclopropylmethyl, the compound becomes a narcotic antagonist.

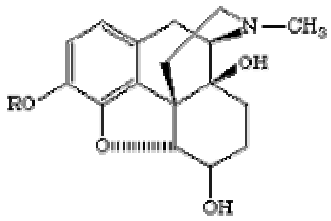
Nuclear (ring) substitutions:

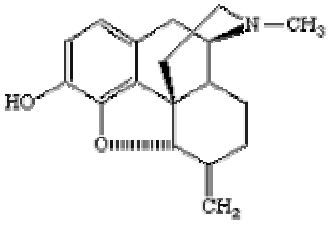
Opening up the ether linkage (E ring) to form the catechol-type ring system shown below will reduce activity by 90%.



0.1 X the potency of morphine

Addition of a 14-beta-OH results in a dramatic increase in activity in the dihydromorphinone series, as shown below.



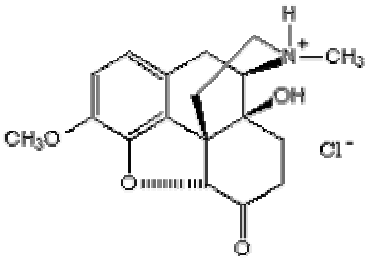


R = H, oxymorphone (10 X morphine)
R = CH3, oxycodone (about equal to morphine)

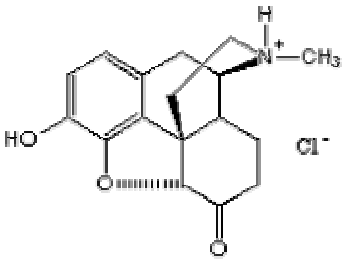
6-methylene-dihydromorphine (80 X morphine)

If the 6 position is substituted with a methylene substituent, as in the structure above (6-methylene-dihydromorphine), the resulting analogue has 80 times the potency of morphine.

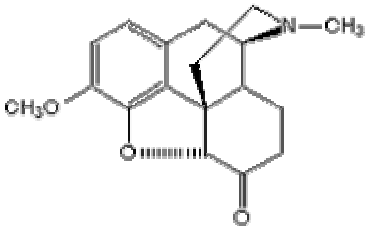
Representative Morphine Analogues



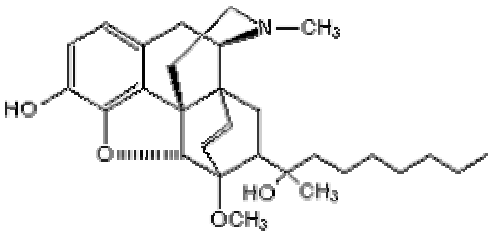
oxycodone HCl (Percodan®, Tylox®)



dihydromorphinone HCl (Dilaudid®)



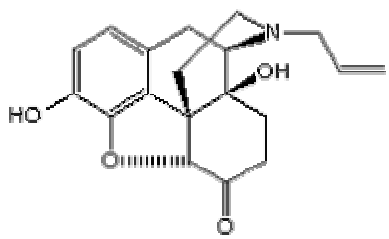
Hydrocodone (Vicodin®)



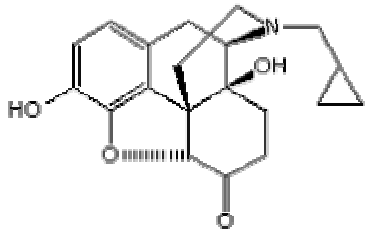
etorphine (Immobilon®)
an oripavine

The oripavine derivative etorphine is a representative of a particularly potent class of morphine analogues. Etorphine is approximately 1000 times as potent as morphine, and arguably is too potent to be released for human therapy. It is currently used as a tranquilizer for large animals.

There are two agents in the morphine class which are marketed as morphine antagonists. These agents, naloxone and naltrexone, are shown below. Naloxone is a pure antagonist, and is commonly used to treat narcotic overdose. Naltrexone is a similar agent, but does possess weak agonist activity, and is used to treat former narcotic addicts.



naloxone (Narcan®)



naltrexone (Trexan®)

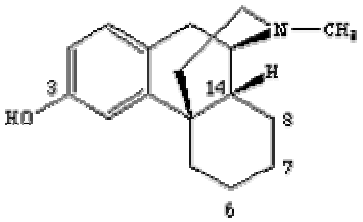
The Morphine Rule

The following structural features are found in most opioid analgesic analogues, and are collectively referred to as the "Morphine Rule". As you will see later, there are some exceptions to this rule.

1. A tertiary nitrogen with a small alkyl substituent.
2. A quaternary carbon.
3. A phenyl group or its isoteric equivalent directly attached to the quaternary carbon.
4. A 2 carbon spacer between the quaternary carbon and the tertiary nitrogen.

Structure/Activity Relationships of Morphinans

The morphinans, which were first introduced by Grewe in 1946, are similar in structure to the morphine analogues, but lack the E ring found in the naturally occurring opioids, as well as the 6-OH and the 7,8-double bond. Their general structure is represented by levorphanol, which is shown below.



levorphanol (LevoDromeran®)
5 X as active as morphine

The structure/activity relationships of the morphinans are very similar to those of the morphines:

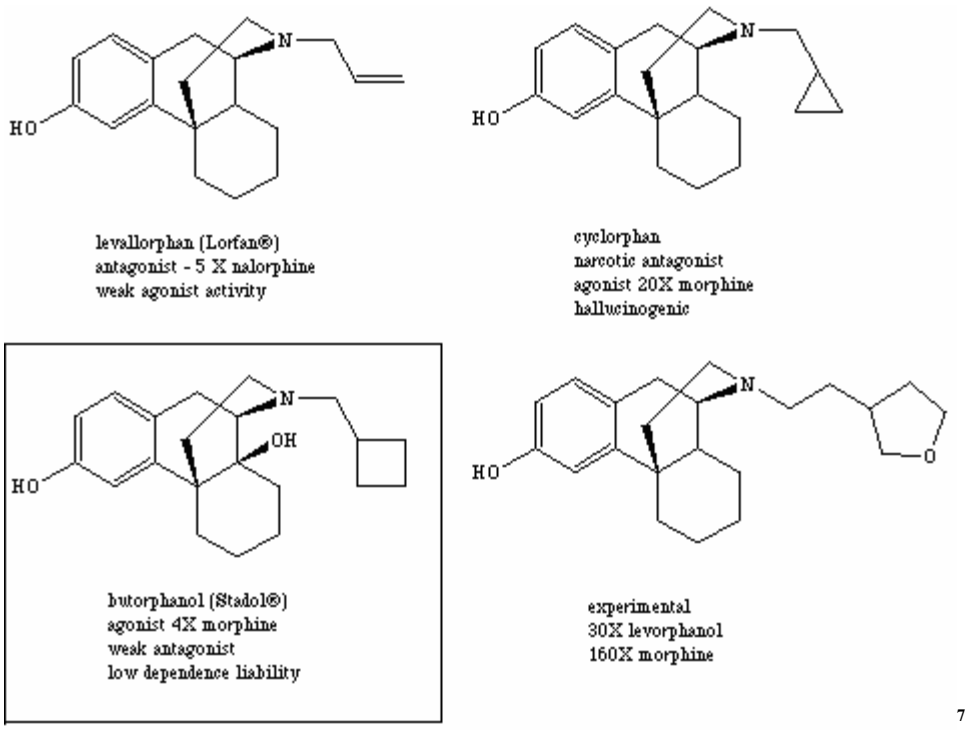
A 3-OH is optimal, and a 3-methoxy is less active.

The nitrogen substituent produces the same activity as in the morphines.

No other substituents may be added to the A ring.

The C ring must be unsubstituted.

Representative Morphinan Analogues



[7]

Specific Uses:
Prior to surgery, veterinarians commonly require the use of anesthetics in order to help the animal cope with the pain. These drugs are only allowed to be administered by a licensed practitioner through prescription only. The farmer cannot single-handedly authorize these drugs for livestock.

Reacting directly with the central nervous system, butorphanol in the form of butorphanol tartrate, eases pain and allows for the veterinarian to proceed with the necessary surgery.

Humans are also given a form of butorphanol tartrate as an anesthetic as well as in nasal spray form to treat migraine headaches.

Action:
Butorphanol acts as an agonist at kappa-opioid receptors and a mixed agonist-antagonist at mu-opioid receptors in the CNS to alter the perception of pain. The drug is believed to act at sites in the periventricular and periaqueductal gray matter, and at sites in the spinal cord.

In contrast to morphine or meperidine, butorphanol produces respiratory depression in a limited dose range, reaching a plateau at approximately 4 mg. The magnitude of respiratory depression with butorphanol is not appreciably increased at a dose of 4 mg; however, the duration of respiratory depression appears to be dose-related.[8]

It binds to opiate receptors at sites in the central nervous system and alters perception and response to pain. It also has the ability to act as an antitussive. With the duration of action lasting about 4 hours, butorphanol

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[7] *Chemistry of Opioid Analgesics*. PHA 422 - Neurology Pharmacotherapeutics
http://wizard.pharm.wayne.edu/medchem/opioid.html

[8] *STADOL NS™ Bristol-Myers Squibb Butorphanol Tartrate Analgesic.*
http://www.rxmed.com/rxmed/b.main/b2.pharmaceutical/b2.1.monographs/cps-%20monographs/cps-%20(general%20monographs-%20s)/stadol%20ns.html

is absorbed in the gut with its highest distribution levels being in the kidney, liver, and intestine. Levels throughout other tissues are found to be higher than plasma. The drug metabolizes in the liver, crosses the placental barrier, distributes into breast milk, is excreted in urine and bile, and then eliminated in the feces.[9]

Combinations:

Torbugesic and oxymorphone are often used on animals by veterinarians one after the other. Since torbugesic is a mu antagonist and oxymorphone is a mu agonist, timing is important because the torbugesic will reverse the oxymorphone if they are injected simultaneously.[10]

Butorphanol is often used in combination with Xylazine, both injected intravenously, in order to obtain sedation.

Butorphanol is also used alongside Detomidine (injected intravenously) in order to sedate the animal prior to surgery.

During halothane anesthesia, if butorphanol is administered simultaneously, then the mean arterial pressure (MAP) is reduced in the patient.

Butorphanol along side naloxone becomes antagonized.

Acepromazine along with butorphanol and xylazine, all administered intravenously, can result in profound sedation for standing restraint.[11]

In pigeons, diazepam and midazolam are sedatives with no analgesic activity and minimal effects upon the cardiac system. They are useful for minimizing anxiety, excitement, and improving restraint. They also provide good muscle relaxation and are very useful in combination with butorphanol for analgesia and sedation.[12]

Status

Historic Use by Organic Farmers:

Felines: Torbugesic-SA® is a potent analgesic that relieves pain caused by major or minor trauma and surgical procedures. It produces its effects within 20 minutes and relieves the pain for up to 8 hours. It provides analgesia with a lower incidence and/or intensity of adverse reactions than traditional opioids. It is not recommended for pregnant cats or kittens under 4 months of age. [13]

Pigeons: Butorphanol is used for sedation and analgesia along with midazolam.[14]

Swine: Administration of butorphanol tartrate allows pigs to rest more peacefully after farrowing. It should be known that there are no analgesics approved for use in swine. This was just noted in an experiment conducted on sows. The use of butorphanol is further impaired because it is a controlled substance.[15]

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[9] *Butorphanol.* http://www.kuddlykorner4u.com/Butorphanol.html
[10] Richey, Meghan. *A Painless Approach to Pain Management.* http://www.vspn.org/VSPNSearch/VSPNLibrary/VSPN001101.htm
[11] *Equine Anesthesia*. http://lam.vet.uga.edu/LAM/LM000084.HTML
[12] *Guidelines for Anesthesia and Analgesia in Pigeons.* University of Michigan. http://216.239.51.100/search?q=cache:ZZOSbi21picC:www.ulam.um...
[13] Wyeth: Products: Animal Health Products. *Torbuigesic-SA®.* http://www.wyeth.com/products/ahp_products/ahp_torbugesic.asp
[14] *Guidelines for Anesthesia and Analgesia in Pigeons.* University of Michigan. http://216.239.51.100/search?q=cache:ZZOSbi21picC:www.ulam.um
[15] Lay, D.C. Jr. and M.F. Haussmann. *Effect of Ibuprofen Administration on Postural Changes in Post-Parturient Sows.* Iowa State University.

Equine: Butorphanol is a pain-relieving agent used in horses to treat colic and postpartum pain. Used intravenously and distributed as a sterile solution, it can also be used as a tranquilizer. It is often used alongside Xylazine in order to provide increased analgesic effects.[16]

Camelids: Butorphanol is used alongside xylazine as an anesthetic prior to castration. For recumbency, it is also administered with xylazine nad ketamine.[17]

Cattle: Combinations of xylazine and butorphanol have been used in cattle to provide neuroleptanalgesia. Doses are 0.01 - 0.02 mg/kg IV of each drug given separately in cattle. Duration of action is approximately 1 hour. Combinations of detomidine (0.07 mg/kg) and butorphanol (0.04 mg/kg) have also been used to immobilize free ranging cattle.[18]

Humans: Known as Stadol® for humans, butorphanol tartrate is a narcotic agonist/antagonist. It is used both parenterally and nasally to cure moderate to severe pain, especially after surgery. The parenteral treatment is used as preoperative medication for pain during labor. The nasal treatment is used for relief of migraine headaches.[19]

OFPA, USDA Final Rule:

OFPA states in Sec. 6509(d):

(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. [20]

Butorphanol is found as butorphanol tartrate in many medications such as Stadol®, which is used in humans, and Torbugesic®, which is used in animals. It is a prescription drug that can only be administered by a licensed practitioner. It is usually administered intravenously to the patient prior to surgery as an anesthetic. There are some nasal forms that are predominantly used in response to migraine headaches in humans.

Policies issued by the FDA:

Note: The following ruling discusses the regulated dosages allotted for butorphanol tartrate tablets.

TITLE 21--FOOD AND DRUGS

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

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[16] Horse-Stores.com *Medications and Supplements: "Butophanol."* http://www.e-stable.com/meds.asp?name=Butorphanol&aka=Torbugesic

[17] *Castration of Camelids: When, Where, Why*. http://www.vet.ohio-state.edu/docs/ClinSci/camelid/castrate.html

[18] *Anesthetic Management of Cattle*. http://www.ivis.org/advances/Steffey_Anesthesia/riebold_cow/chapter_frm.asp

[19] *Butorphanol Tartrate.* http://www.nursespdr.com/members/databse/ndrhtml/butorphanoltar...

[20] *6509 Animal Production Practices and Materials.* Federal Organic Food Production Act of 1990. http://www.ams.usda.gov/nop/orgact/htm

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

Sec. 520.**246** Butorphanol tartrate tablets.

(a) Specifications. Each tablet contains 1, 5, or 10 milligrams of butorphanol base activity as butorphanol tartrate.
(b) Sponsor. See No. 000856 in Sec. 510.600(c) of this chapter.
(c) Conditions of use. The drug is used for the treatment of dogs as follows:
(1) Amount. 0.25 milligram of butorphanol base activity per pound of body weight.
(2) Indications for use. For the relief of chronic nonproductive cough associated with tracheo-bronchitis, tracheitis, tonsillitis, laryngitis, and pharyngitis associated with inflammatory conditions of the upper respiratory tract.
(3) Limitations. For oral use in dogs only. Repeat at intervals of 6 to 12 hours as required. If necessary, increase dose to a maximum of 0.5 milligram per pound of body weight. Treatment should not normally be required for longer than 7 days. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

[47 FR l4702, Apr. 6, 1982, as amended at 53 FR 27851, July 25, 1988]

Note: The following FDA rule discusses the regulated dosages allotted for butorphanol tartrate injections.

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.**246** Butorphanol tartrate injection.

(a) Specifications. Each milliliter of aqueous solution contains either 0.5, 2 or 10 milligrams of butorphanol (as butorphanol tartrate).
(b) Sponsors. Approval to firms identified in Sec. 510.600(c) of this chapter for use as indicated:
(1) See No. 057926 for use as in paragraph (c)(2) of this section.
(2) See No. 000856 for use as in paragraphs (c)(1), (c)(2), and (c)(3) of this section.
(c) Conditions of use--(1) Dogs--(i) Amount. 0.025 milligram of butorphanol base activity per pound of body weight (equivalent to 0.5 milliliter per 10 pounds), using 0.5 milligram per milliliter solution.
(ii) Indications for use. For the relief of chronic nonproductive cough associated with tracheo-bronchitis, tracheitis, tonsillitis, laryngitis, and pharyngitis associated with inflammatory conditions of the upper respiratory tract.
(iii) Limitations. For subcutaneous injection in dogs only. Repeat at intervals of 6 to 12 hours as required. If necessary, increase dose

to maximum of 0.05 milligram per pound of body weight. Treatment should not normally be required for longer than 7 days. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

(2) Horses--(i) Amount. 0.05 milligram of butorphanol base activity per pound of body weight (0.1 milligram/kilogram) using 10 milligrams per milliliter solution.

(ii) Indications for use. For the relief of pain associated with colic and postpartum pain in adult horses and yearlings.

(iii) Limitations. For intravenous use in horses only. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours. Not for use in horses intended for food. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

(3) Cats--(i) Amount. 0.2 milligram of butorphanol base activity per pound of body weight (0.4 milligram/kilogram), using 2 milligrams per milliliter solution.

(ii) Indications for use. For the relief of pain in cats caused by major or minor trauma, or pain associated with surgical procedures.

(iii) Limitations. For subcutaneous injection in cats only. Dose may be repeated up to 4 times per day. Do not treat for more than 2 days. Safety for use in pregnant female cats, breeding male cats or kittens less than 4 months of age has not been determined. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

[45 FR 29276, May 2, 1980, as amended at 50 FR 24508, June 11, 1985; 53 FR 27851, July 25, 1988; 59 FR 41665, Aug. 15, 1994; 63 FR 66432, Dec. 2, 1998]

Note: The following law pertains to the place of butorphanol on Schedule II of controlled substances. Relevant information 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.**12** Schedule II.

(a) Schedule II 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 Controlled Substances Code Number set forth opposite it.

(b) Substances, vegetable origin or chemical synthesis. Unless specifically excepted or unless listed in another schedule, any of the following substances whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis:

(1) Opium and opiate, and any salt, compound, derivative, or preparation of opium or opiate excluding apomorphine, thebaine-derived butorphanol, dextrorphan, nalbuphine, nalmefene, naloxone, and naltrexone, and their respective salts, but including the following:

(1) Raw opium..... 9600
(2) Opium extracts..... 9610
(3) Opium fluid..... 9620
(4) Powdered opium..... 9639
(5) Granulated opium..... 9640
(6) Tincture of opium..... 9630
(7) Codeine..... 9050
(8) Dihydroetorphine..... 9334
(9) Ethylmorphine..... 9190
(10) Etorphine hydrochloride..... 9059
(11) Hydrocodone..... 9193
(12) Hydromorphone..... 9150
(13) Metopon..... 9260
(14) Morphine..... 9300
(15) Oxycodone..... 9143
(16) Oxymorphone..... 9652
(17) Thebaine..... 9333

(2) Any salt, compound, derivative, or preparation thereof which is chemically equivalent or identical with any of the substances referred to in paragraph (b) (1) of this section, except that these substances shall not include the isoquinoline alkaloids of opium.

(3) Opium poppy and poppy straw.

(4) Coca leaves (9040) and any salt, compound, derivative or preparation of coca leaves (including cocaine (9041) and ecgonine (9180) and their salts, isomers, derivatives and salts of isomers and derivatives), and any salt, compound, derivative, or preparation thereof which is chemically equivalent or identical with any of these substances, except that the substances shall not include decocainized coca leaves or extraction of coca leaves, which extractions do not contain cocaine or ecgonine.

(5) Concentrate of poppy straw (the crude extract of poppy straw in either liquid, solid or powder form which contains the phenanthrene alkaloids of the opium poppy), 9670.

(c) Opiates. Unless specifically excepted or unless in another schedule any of the following opiates, including its isomers, esters, ethers, salts and salts of isomers, esters and ethers whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, dextrorphan and levopropoxyphene excepted:

(1) Alfentanil..... 9737
(2) Alphaprodine..... 9010
(3) Anileridine..... 9020
(4) Bezitramide..... 9800
(5) Bulk dextropropoxyphene (non-dosage forms)..... 9273
(6) Carfentanil..... 9743
(7) Dihydrocodeine..... 9120
(8) Diphenoxylate..... 9170
(9) Fentanyl..... 9801
(10) Isomethadone..... 9226
(11) Levo-alphacetylmethadol..... 9648
[Some other names: levo-alpha-acetylmethadol, levomethadyl acetate, LAAM]
(**12**) Levomethorphan..... 9210
(13) Levorphanol..... 9220

(14) Metazocine..... 9240
(15) Methadone..... 9250
(16) Methadone-Intermediate, 4-cyano-2-dimethylamino-4,4-diphenyl 9254
butane.....
(17) Moramide-Intermediate, 2-methyl-3-morpholino-1, 1- 9802
diphenylpropane-carboxylic acid.....
(18) Pethidine (meperidine)..... 9230
(19) Pethidine-Intermediate-A, 4-cyano-1-methyl-4- 9232
phenylpiperidine.....
(20) Pethidine-Intermediate-B, ethyl-4-phenylpiperidine-4- 9233
carboxylate.....
(21) Pethidine-Intermediate-C, 1-methyl-4-phenylpiperidine-4- 9234
carboxylic acid.....
(22) Phenazocine..... 9715
(23) Piminodine..... 9730
(24) Racemethorphan..... 9732
(25) Racemorphan..... 9733
(26) Remifentanil..... 9739
(27) Sufentanil..... 9740

(d) 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:

(1) Amphetamine, its salts, optical isomers, and salts of its 1100
optical isomers.....
(2) Methamphetamine, its salts, isomers, and salts of its isomers 1105
(3) Phenmetrazine and its salts..... 1631
(4) Methylphenidate..... 1724

(e) Depressants. 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 depressant effect on the central nervous system, 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) Amobarbital..... 2125
(2) Glutethimide..... 2550
(3) Pentobarbital..... 2270
(4) Phencyclidine..... 7471
(5) Secobarbital..... 2315

(f) Hallucinogenic substances.

(1) Nabilone..... 7379
[Another name for nabilone: ()-trans-3-(1,1-
dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-
dimethyl-9H-dibenzo[b,d]pyran-9-one]

(g) Immediate precursors. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances:
(1) Immediate precursor to amphetamine and methamphetamine:

(i) Phenylacetone..... 8501
Some trade or other names: phenyl-2-propanone; P2P; benzyl methyl ketone; methyl benzyl ketone;

(2) Immediate precursors to phencyclidine (PCP):

(i) 1-phenylcyclohexylamine..... 7460
(ii) 1-piperidinocyclohexanecarbonitrile (PCC)..... 8603

[39 FR 22142, June 20, 1974]

Note: The following law pertains to the place of butorphanol on Schedule IV of controlled substances. Relevant information 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) Estazolam..... 2756
(16) Ethchlorvynol..... 2540
(17) Ethinamate..... 2545
(18) Ethyl loflazepate..... 2758
(19) Fludiazepam..... 2759
(20) Flunitrazepam..... 2763
(21) Flurazepam..... 2767
(22) Halazepam..... 2762
(23) Haloxazolam..... 2771
(24) Ketazolam..... 2772
(25) Loprazolam..... 2773
(26) Lorazepam..... 2885
(27) Lormetazepam..... 2774
(28) Mebutamate..... 2800
(29) Medazepam..... 2836
(30) Meprobamate..... 2820
(31) Methohexital..... 2264
(32) Methylphenobarbital (mephobarbital)..... 2250
(33) Midazolam..... 2884
(34) Nimetazepam..... 2837
(35) Nitrazepam..... 2834
(36) Nordiazepam..... 2838
(37) Oxazepam..... 2835
(38) Oxazolam..... 2839
(39) Paraldehyde..... 2585
(40) Petrichloral..... 2591
(41) Phenobarbital..... 2285
(42) Pinazepam..... 2883
(43) Prazepam..... 2764
(44) Quazepam..... 2881
(45) Temazepam..... 2925
(46) Tetrazepam..... 2886
(47) Triazolam..... 2887
(48) Zaleplon..... 2781
(49) 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][21]

Regulatory: EPA/NIEHS/Other Sources
ACGIH: None
CERCLA: Not Listed
IARC: None
EPA: Nothing particular listed.
NIEHS: Nothing specific.
NIOSH: No relevant information directly pertaining to butorphanol.
NOSB: Butorphanol material is scheduled to be petitioned in September 2002
Category: Livestock
Petitioned Use of Material: Anesthetic
NTP: No
OSHA: Not Regulated[22]
RCRA: Not Listed
SARA: Not Listed in 313

Status Among U.S. Certifiers
NOFA: "The following medications are allowed with a 5 day withholding:

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[21] 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
[22] *Material Safety Data Sheet*. Bedford Laboratories. http://216.239.37.100/search?q=cache:NphtFBAwZG0C:www.bedfordlabs.com/msds/Butorph%2520Preserv.pdf+butorphanol+AND+melting+point&hl=en&ie=UTF8

- non-steroidal anti-flammatory (i.e. banamine)
- antihistamines (e.g. epinephrine, adrenaline)
- anesthetics"[23]

Pennsylvania/Minnesota/Oregon: Go along with the OMRI status. Butorphanol is a synthetic drug currently under consideration according to the OMRI.

International

IFOAM Basic Standards:

5.7. Veterinary Medicine

General Principles

Management practices should be directed to the well being of animals, achieving maximum resistance against disease and preventing infections.

Sick and injured animals must be given prompt and adequate treatment.

Recommendations

Natural medicines and methods, including homeopathy, ayurvedic medicine and acupuncture, should be emphasised.

When illness does occur the aim should be to find the cause and prevent future outbreaks by changing management practices.

Where appropriate the certification bodies should set conditions based on the farm's veterinary records to minimise the use of medicines.

The certification body/ standardising organisation should make a list of medicines and withholding periods.

Standards

5.7.1.

The well-being of the animals is the primary consideration in the choice of illness treatment. The use of conventional veterinary medicines is allowed when no other justifiable alternative is available.

5.7.2.

Where conventional veterinary medicines are used, the withholding period shall be at least double the legal period.[24]

Canadian General Standards: Canadian General Standards: Canada possesses 3 standards of beef—natural beef, certified organic beef, and certified hormone-free beef. Natural beef consists of beef that has not been treated with antibiotics or hormones. [25]

European Union: Butorphanol tartrate is included as an Annex II type drug (Reg. 1076/98). This means that it is permitted for use in veterinary medicine as of January 1, 2000. [26]

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.*

[23] VOF Organic Meat & Egg Production – NOFA Vermont http://www.nofavt.org/sht02_stds7.cfm
[24] *IFOAM Basic Standards 2000* http://www.ifoam.org/standard/basics.html#10
[25] Canada Beef Export Federation February 2001 http://www.agric.gov.ab.ca/agdex/400/420_830-3.pdf
[26] Status of MRL Procedures. *MRL assessments in the context of Council Regulation (EEC) No. 2377/90.* http://www.emea.eu.int/pdfs/vet/srwp/076599en.pdf

Butorphanol may interact with other medications. Consult with a veterinarian to determine if other drugs the pet is receiving could interact with butorphanol. Such drugs include tranquilizers, barbiturates, and antihistamines.[27]

If used with other central nervous system depressants, butorphanol may increase the CNS or respiratory depression of those drugs. It is recommended to decrease butophanol's dosage if used in conjunction with those particular drugs. [28]

Butorphanol does not seem to interact with anything in a dangerous manner, nor does it seem to break down into harmful components. Although it is synthetic, the body can break it down in a matter of hours and excrete harmless remnants of the drug through the feces. For safety sake, there are particular withdrawal times that should be observed by the farmer in order to make the meat derived from these animals safe for eating.

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.*

Section X

STABILITY AND REACTIVITY DATA
Stability:
Stable
Incompatibility (Materials to Avoid):
Strong oxidizers and water reactive materials
Hazardous Decomposition or Byproducts:
As with any burning material, carbon monoxide,
carbon dioxide, nitrogen oxides, and sulfur oxides may be produced.
Hazardous Polymerization:
Will not occur.
Conditions to Avoid:
Storage with oxidizers and water reactive materials

Section XI

TOXICOLOGICAL INFORMATION
For **Butorphanol** Tartrate (active ingredient):
LD 50 rat, oral = 315 mg/kg
LD 50 mouse, intramuscular = 208 mg/kg
LD 50 rat, intraperitoneal = 127 mg/kg
LD 50 dog, intravenous = 10 mg/kg
LD 50 rat, subcutaneous = 425 mg/kg
LD 50 dog, intramuscular = 17 mg/kg
LD 50 rat, intravenous = 17 mg/kg
LD 50 mouse, intravenous = 36 mg/kg
LD 50 rat, intramuscular = 255 mg/kg
LD 50 mouse, oral = 395 mg/kg
LD 50 mouse, intraperitoneal = 192 mg/kg
LD 50 mouse, subcutaneous = 299 mg/kg

Safety in pregnant and very young animals has not been determined.

[27] *Butorphanol Tartrate.* http://petplace.netscape.com/netscape/nsArtShow.asp?artID=1560
[28] *Butorphanl*. http://www.kuddlykorner4u.com/Butorphanol.html

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

Section V

FIRE AND EXPLOSION HAZARD DATA
Flash Point (Method Used):
Not Applicable
LEL:
Not Applicable
UEL:
Not Applicable
Extinguishing Media:
Use water or a type ABC multi-purpose extinguisher.
Special Fire Fighting Procedures:
As with all fires, evacuate personnel to a safe area. Firefighters should wear self-contained breathing apparatus to avoid smoke inhalation. Product is aqueous-based and is not expected to present a fire hazard concern.
Unusual Fire/Explosion Hazards:
NONE

Section VI

ACCIDENTAL RELEASE INFORMATION
Release to Land:
Absorb **Butorphanol** with sorbent materials and dispose of according to local, state, and federal guidelines.
Release to Air:
If aerosolized, reduce exposures by ventilating area; clean up spill immediately to prevent evaporation.
Release to Water:
Refer to local water authority. Drain disposal is not recommended; however, refer to local, state, and federal disposal guidelines

ENVIRONMENTAL IMPACT INFORMATION
Information is currently not available on the environmental impact of **Butorphanol** Tartrate. Handle in a manner to prevent spills or releases to the environment.

Section XIII

DISPOSAL INFORMATION
Dispose of as a Schedule IV Controlled Substance according to DEA Guidelines.
Dispose of by incineration at an approved/permitted incinerator.
Review local, state, and federal regulations for your regulatory area.

Section XIV

TRANSPORTATION INFORMATION
Butorphanol Tartrate Injection, USP is not a DOT hazardous material.
Butorphanol is not a Marine Pollutant.

OTHER DATA
1. Use of this product should be through or under the direction of a physician.
This MSDS does not address the therapeutic use of this material.
2. Persons administering this drug to patients must be careful to avoid needle sticks to syringes and

other sharps used in the administration. All needle sticks must be reported to your company management.[29]

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

As a morphinan analogue, butorphanol has been proven in to be addictive and should therefore not be misused. The following article discusses the health effects of butorphanol, focusing on the legal aspect and the placement of it in Schedule IV:

Regulation Watch

Moshe Shalev, MSc, VMD, Column Editor

Drug Enforcement Administration Places Butorphanol into Schedule IV

On September 22, the Acting Deputy Administrator of the Drug Enforcement Administration (DEA) of the Department of Justice placed butorphanol (including its salts and optical isomers) into Schedule IV of the Controlled Substances Act (CSA). As of October 31, the manufacture, distribution, dispensation, importation, and exportation of butorphanol (and all products containing butorphanol) are subject to the regulatory controls and criminal sanctions of Schedule IV.

Butorphanol, an opioid agonist-antagonist analgesic, is marketed as a veterinary product under the trade names "Torbugesic" and "Torbutrol" for use in horses and dogs. The use of butorphanol in veterinary medicine, particularly laboratory animals, has increased considerably in recent years. This trend is due to the social consciousness and regulatory requirements surrounding appropriate post-operative care of animals; the ease of obtaining this drug; and its effective, safe, and prolonged analgesic effects in many animal species.

Doctors prescribe butorphanol ("Stadol") for the relief of moderate-to-severe pain in humans. Butorphanol first appeared on the market as an injectable product in 1979. Although there was limited abuse of the injectable drug among certain populations, the use of the nasal spray since 1992 has resulted in significant abuse.

Considering the scientific and medical information, and the recommendations of the Assistant Secretary for Health, the Acting Deputy Administrator of the DEA found that:

1. Butorphanol has a low potential for abuse, relative to the other drugs or substances in Schedule III;
2. Butorphanol has an accepted medical use in the United States;
3. Abuse of butorphanol may lead to limited physical and psychological dependence, relative to the other drugs or substances in Schedule III.

The Schedule IV regulations that now apply to butorphanol are:

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[29] *Material Safety Data Sheet*. Bedford Laboratories. http://216.239.37.100/search?q=cache:NphtFBAwZG0C:www.bedfordlabs.com/msds/Butorph%2520Preserv.pdf+butorphanol+AND+melting+point&hl=en&ie=UTF8

Registration: Any person who manufactures, distributes, dispenses, imports, or exports butorphanol; engages in research or conducts instructional activities with butorphanol; or proposes to engage in such activities, must submit an application for Schedule IV registration, in accordance with Part 1301 of Title 21 of the *Code of Federal Regulations*. Any person who is currently lawfully engaged in any of the above activities must have submitted an application for registration by October 31; he or she may continue his or her lawful activities until the DEA has approved or denied the application.

Security: Butorphanol must be manufactured, distributed, and stored in accordance with Secs. 1301.71; 1301.72(b), (c), and (d); 1301.73; 1301.74; 1301.75(b) and (c); and 1301.76 of Title 21 of the *Code of Federal Regulations*.

Labeling and Packaging: All labels on commercial containers of, and all labeling of butorphanol distributed on and after April 1, 1998, shall comply with the requirements of Secs. 1302.03-1302.07 of Title 21 of the *Code of Federal Regulations*. Any commercial containers of butorphanol packaged on or before April 1, 1998, and not meeting the requirements specified in Secs. 1302.03-1302.07 of Title 21 of the *Code of Federal Regulations*, shall not be distributed on or after July 1, 1998.

Inventory: Registrants possessing butorphanol must take inventories pursuant to Secs. 1304.03, 1304.04, and 1304.11 of Title 21 of the *Code of Federal Regulations*.

Records: All registrants must keep records pursuant to Secs. 1304.03, 1304.04, and 1304.21-1304.23 of Title 21 of the *Code of Federal Regulations*.

Prescriptions: All prescriptions for butorphanol must be issued pursuant to Secs. 1306.03-1306.06 and 1306.21-1306.26 of Title 21 of the *Code of Federal Regulations*. All prescriptions for products containing butorphanol issued on or before October 31, if authorized for refilling, shall, as of that date, be limited to five refills, and shall not be refilled after April 1, 1998.

Importation and Exportation: All importation and exportation of butorphanol shall be in compliance with Part 1312 of Title 21 of the *Code of Federal Regulations*.

Criminal Activity: Any activity with butorphanol not authorized by, or in violation of, the CSA or the Controlled Substances Import and Export Act shall be unlawful on or after October 31.

The Acting Deputy Administrator, in accordance with the Regulatory Flexibility Act [5 U.S.C. 605(b)], has reviewed this proposed rule and, by approving it, certified that it will not have a significant economic impact on a substantial number of small-business entities; will not significantly or uniquely affect small governments; will not cause a major increase in costs or prices; will not have significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of the US-based companies to compete with foreign-based companies in domestic and export markets; and in accordance with E.O. 12612, this rule will not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

Within laboratory animal medicine, classifying butorphanol (including its salts and optical isomers) as a Schedule IV drug may cause significant hardship, due to the popularity of the drug as a post-operative analgesic, and the fact that investigators must now obtain a license to legally use it. However, in the event that Schedule IV classification imposes special hardships on the

registrants, the DEA will entertain any justified request for an extension of time to comply with the regulations. [30]

Safe use during pregnancy, during labor for premature infants, or in children under 18 has not been established. Use with extreme caution in clients with AMI, ventricular dysfunction, and coronary insufficiency (morphine or meperidine are preferred). Use in clients physically dependent on narcotics will result in precipitation of a withdrawal syndrome. Geriatric clients may be more sensitive to side effects, especially dizziness. [31]

Section III

HEALTH HAZARD DATA
Routes of Entry:
Exposure may occur via inhalation, ingestion, or absorption through the skin or eyes. Product is a morphine derivative used as an analgesic.
Health Hazard (Acute & Chronic):
Butorphanol affects the central nervous system, depresses respiratory activity, and produces sedation. Product may also affect the circulatory, digestive, and urinary tract systems. May cause irritation and allergic reaction.
Carcinogenicity:
NTP?
NO
IARC Monographs?
NONE
OSHA Regulated?
NO

Signs & Symptoms of Exposure:
May cause tiredness, dizziness, unconsciousness, nausea, vomiting, constipation, abdominal pain, heart palpitations, sweating/clammy skin, skin rashes, hallucinations, euphoria, visual disturbances, headache, pinpoint pupils. May cause irritation.
Medical Conditions Generally Aggravated by Exposure:
Persons with respiratory and circulatory problems, liver or kidney disease physical dependence on narcotics and hypersensitivity to butorphanol may have more severe effects from exposure.
BVL Hazard Category: 3

Section IV

FIRST AID MEASURES
Eye Exposure:
Flush eyes with large volumes of water for 15 or more minutes.
Skin Exposure:
Wash skin with cool, soapy water for 15 minutes.
Ingestion:
Seek medical attention from a physician immediately. Induce vomiting if person is conscious. Never induce vomiting on an unconscious person.
Inhalation:
If difficulty breathing, administer oxygen. Seek attention of a physician immediately. If necessary, provide artificial respiration.

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[30] *Regulation Watch. "Drug Enforcement Administration Places Butorphanol into Schedule IV"* http://www.labanimal.com/col/reg1097.htm
[31] *Butorphanol Tartrate.* http://www.nursespdr.com/members/databse/ndrhtml/butorphanoltartrate

Overdose should be treated symptomatically to maintain airway

Section VII

PRECAUTIONS FOR SAFE HANDLING AND USE
Steps to be taken in case material is released or spilled:
See Section VI above. Wear latex or nitrile gloves and safety glasses when cleaning spills. A dust/mist respirator (N95) may be necessary if excessive aerosols are generated.
Waste Disposal Method:
Incineration in an approved/permitted incinerator is recommended.
Refer to local, state, and federal rules.
Precautions to be taken in handling and storing:
Store at room temperature (<86°F).
Other Precautions:
Take care to prevent aerosolization of product.

Section VIII

CONTROL MEASURES AND PERSONAL PROTECTIVE EQUIPMENT
Respiratory Protection:
Under normal use, respirators are not required. If aerosols are generated, a disposable dust/mist respirator (N95) may be used. Personnel wearing respirators should be fit tested and approved for respirator use under the OSHA Respiratory Protection Standard 29 CFR 1910.134.
Ventilation:
Handle product in a well-ventilated area.
Protective Gloves:
Nitrile or latex
Eye Protection:
Safety glasses
Other Protective Clothing or Equipment:
Lab coat
Work/Hygienic Practices:
Wash hands following use. No eating, drinking, or smoking when handling this product.[32]

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.*

While generally safe and effective when prescribed by a veterinarian, butorphanol can cause side effects in some animals:

It should not be used in animals with known hypersensitivity or allergy to the drug and it should be used with caution in animals with an under active thyroid, kidney impairment, elderly or severe illness. Butorphanol should also be avoided in animals with head trauma or nervous system dysfunction. The most significant side effects associated with butorphanol are sedation, lack of appetite, and diarrhea.[33]

Adverse Reactions:
CNS: sedation, confusion, lethargy, agitation

[32] *Material Safety Data Sheet*. Bedford Laboratories. http://216.239.37.100/search?q=cache:NphtFBAwZG0C:www.bedfordlabs.com/msds/Butorph%2520Preserv.pdf+butorphanol+AND+melting+point&hl=en&ie=UTF8
[33] *Butorphanol Tartrate.* http://petplace.netscape.com/netscape/nsArtShow.asp?artID=1560

CV: bradycardia
Respiratory: decreased respiratory rate
GI: constipation
GU: urinary retention
Skin: itching
Other: In the event of signs of overdose, such as cardiac and respiratory depression, administer naloxone 0.01 to 0.10 mg/kg SC, IP (narcotic reversal), fluids, O_2, and vasopressors.[34]

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

Butorphanol belongs to a general class of drugs known as opiate agonists. It is commonly used as an anesthetic used to treat patients prior to surgery. Other related drugs in this class include buprenorphine, fentanyl, merperidine, and morphine.[35]

Xylazine, Acepromazine, and Butorphanol serve similar functions but each has its own specific advantages that make it the preferred treatment at the time: Acepromazine has no analgesic activity, it is only a sedative; Xylazine has both analgesic and sedative properties; Butorphanol is a pain killer with no real sedative activity.

7. *Its compatibility with a system of sustainable agriculture.*

Butorphanol has not been proven to be a hazardous drug when used properly. Like other drugs, it should be handled with respect to certain precautions. By using it responsibly, adhering to the given dosages, waiting the allotted legal withdrawal times, and following all instructions with respect to storage, butorphanol should not pose a serious harm. In very rare cases, it has been proven to cause addiction in humans (being a derivative of morphine), but by following the allotted withdrawal times, this should not be a serious threat; thus making it the responsibility of the farmers.

Since butorphanol is only administered by certified veterinarians in emergency surgery, the chances of harmful drug misuse can be regulated. Butophanol has proven to be a drug that is quickly broken down and removed from the animal's bloodstream through urine and therefore, by waiting the adequate withdrawal time prior to slaughter, there is no real threat posed to humans. Once again, there are always precautionary efforts that accompany the use and administration of any drug.

As a synthetic material, butorphanol is under consideration by OFPA provided that it is used according to all the regulations and meets all FDA requirements. Being an anesthetic, butorphanol is used to care for the animals themselves, relieving them from discomfort and pain during veterinary surgery, generally free of sedative effects. If used responsibly, there should be no harm done to the system of sustainable agriculture.

[34] *Butorphanol*. http://www.kuddlykorner4u.com/Butorphanol.html
[35] *Butorphanol Tartrate.* http://petplace.netscape.com/netscape/nsArtShow.asp?artID=1560

TAP Reviewers' Discussion

Reviewer 1: *[M.D., Associate Professor of Medicine, Eastern U.S.]*

Observations/OFPA Criteria
My review will address the criteria listed in 7 USC 6518 where I quote the regulations in italics for clarity with my comments interposed.

7 USC 6518 NATIONAL ORGANIC STANDARDS BOARD.

(m) Evaluation. In evaluating substances considered for inclusion in the proposed National List or proposed amendment to the National List, the Board shall consider

(1) the potential of such substances for detrimental chemical interactions with other materials used in organic farming systems;

There are no detrimental chemical interactions reported to occur with other materials. The milligram (mg) quantities used in treating individual animals are so small trivially small as not to have a potential impact were such interactions identified either in the animal or in the environment. So called interactions that do occur are pharmacodynamic in nature (drug effects on the body) and not chemical. That is, other than the metabolites that the liver makes, which are slightly modified versions of the parent drug and are pharmacologically inert (no drug effect), the "interactions" of butorphanol with other substances used to treat animals or humans are the result of combined drug effects. There is no recombining of butorphanol with other drugs or chemicals to make completely new compounds with different effects.

(2) the toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment;

As licensed by FDA for veterinary use by licensed veterinarians, butorphanol is safe and effective. Its effects on the animal are transient (hours); use is typically only episodic; no residual effects remain after the first day, usually after a few hours. The drug is completely cleared from the animal in less time than is required by law before slaughter of the animal for human consumption. There is no evidence of deleterious effects on the environment from butorphanol or its metabolic products. Further, given the small amounts used in single animals as may contribute to possible contamination of soil and water in the agricultural setting (as opposed to a more intensive veterinary surgical setting where many animals may contribute a larger total amount of butorphanol and metabolic products in the acute post-operative setting) it is implausible that this could have deleterious effects.

I am not aware of specific environmental impact assessments of butorphanol and its metabolites. However, the drug products that are excreted via urine and bile are water-soluble which will not likely accumulate in the local environment. Butorphanol disposal in city water drainage/sewer systems is accepted practice.

(3) the probability of environmental contamination during manufacture, use, misuse or disposal of such substance;

I cannot comment on the environmental risks of manufacturing butorphanol, but the use according to FDA regulation by licensed veterinarians and the proper disposal by the same should not be associated with significant environmental contamination in the agricultural setting. After single dose quantities are used in the animal, the proper disposal is well described under other federal regulations. Typically, this is done by washing down the drain of the veterinary hospital any excess amount of a dose drawn up for dosing and not used in a single animal. This is acceptable to the drug enforcement authorities (DEA) and is not on the list of hazardous chemicals by their report. Larger "lot" sized amounts, such as need to be disposed of when the drug has expired its safe shelf life, are typically incinerated at licensed facilities or under the

supervision of federal or state authorities to be sure the drug is safely destroyed and not diverted to illicit use.

(4) the effect of the substance on human health;

Used as regulated by FDA, butorphanol is safe and effective for human use to treat moderate to severe pain. It exerts its pharmacologic effects primarily in the central nervous system at mu and kappa opiate receptors where it is a partial agonist/antagonist. The drug has a half-life of 4-7 hours, meaning 97% of the drug is removed from the body within 20-35 hours. In excess doses, there are deleterious side effects, including nausea, somnolence, reduced intestinal motility, and possibly respiratory depression. Because butorphanol is a mixed agonist/antagonist, its abuse potential and side effects are less than traditional opiates that are pure opiate receptor agonists, like morphine or heroin. Because there is an abuse potential, it is a scheduled IV (controlled) substance under the control of the Drug Enforcement Administration, but this is a much lower level of control than is in force for true opiates like morphine.

The likelihood of a human receiving a butorphanol dose in food that would result in any effect is exceedingly small. For example, the maximum exposure of a human to butorphanol via consumption of a pound of meat from an animal given the typical butorphanol dose immediately (which never occurs subject to other regulations) prior to slaughter, would be less than 1% of the typical human dose. This makes some assumptions about immediate distribution in the animal, typical absorption in humans, and the recommended doses for analgesia in adult humans. Once one accounts for time of distribution in the animal, metabolism in the animal liver, required 5 day withholding before slaughter, and the slow absorption in man, all of which further reduce the amount a human might be exposed to, there is essentially no chance for any effect in humans.

(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;

There is no available data to suggest that there are biological or chemical interactions in the agroecosystem. To my knowledge, there are no known species which have opiate receptors except for the animal kingdom, so there is no evidence that plants may be affected in any deleterious way. There is no physico-chemical reason to expect there to be salt index or solubility effects on the soil, but neither am I aware of evidence to support or refute this. Were an effect possible, however, given the very small mg quantities used in single animals, the magnitude of effect should be transient and very small. The amounts used in single animals are very rapidly diluted. The drug is metabolized in the animal to water-soluble chemicals which should not accumulate. The metabolites of butorphanol are inert substances medically speaking.

(6) the alternatives to using the substance in terms of practices or other available materials; and

There are non-synthetic opiates available for use, but butorphanol is preferred for several reasons: it is associated with fewer adverse effects for the animal; it has less abuse potential in humans thereby reducing unwanted consequences if the drug is "diverted" to illicit use. It is also preferred by some medical doctors for the same reason reasons.

(7) its compatibility with a system of sustainable agriculture.

Based on the foregoing, it seems the only impact on sustainable agriculture is a positive one through enhancement of the health of animals who need appropriate pre-operative treatment with butorphanol to enable surgical treatment of the animals.

Reviewer 1 Conclusions and Recommendations:

I believe butorphanol should be considered synthetic by nature of its synthetic method of manufacture, but allowed on the list without restrictions other than those governing its lawful use by licensed veterinarians under other federal regulations (namely, FDA and DEA regulations).

Reviewer 2: *[PhD, Animal Science, M.S. Dairy Science. Professor, Department of Animal Sciences. Central U.S.]*

Comments on Database
The following information needs to be corrected or added to the database:
No additional information is required.

Observations/OFPA Criteria
The petition is for inclusion of butorphanol to the National List of Allowed and Prohibited Substances under the Organic Foods Production Act of 1990. Butorphanol is petitioned for addition to the National List as a synthetic substance allowed for use in organic production. The intended use is as a livestock medical treatment, specifically as a synthetic narcotic for surgical procedures, possibly used in combination with xylazine and acepromazine.

The TAP report has covered the important points concerning butorphanol and its value as a synthetic narcotic used as an anesthetic in animals before undergoing surgical procedures.

While the use of medication in the absence of illness is a prohibited health care practice under the Organic Foods Production Act, Sec. 6509(d), the welfare of the animal must be of primary concern in cases of animals undergoing surgery. Surgical procedures for livestock require the use of pain alleviating procedures, including drugs for anesthesia. Butorphanol is an effective anesthetic when used appropriately. Butorphanol is only to be used by a licensed practitioner for administration prior to surgery as an anesthetic. Use of this prescription drug is tightly regulated by the Food and Drug Administration and the Drug Enforcement Agency. Butorphanol is classified as a Schedule IV drug under the DEA Schedule of Controlled Substances. Rulings by FDA include approval of use of butorphanol tartrate tablets as an antitussive in dogs, and butorphanol tartrate injection as an antitussive in dogs, and for relief of pain in horses and cats. Although commonly used in combination with other drugs in cattle, FDA rulings on regulated dosages are not available. Use of butorphanol in swine has been limited.

Several adverse reactions have been noted for butorphanol which may occur in response to overdosing. Use of the drug for surgical procedures by a licensed practitioner must be in accordance with FDA regulated dosages indicated for livestock.

Exposure of the animal handler or practitioner to butorphanol via inhalation, ingestion, or absorption through the skin or eyes is to be avoided. Butorphanol can affect the central nervous system, depress respiratory activity, produce sedation, and affect the circulatory, digestive and urinary tract systems, resulting in a range of symptoms.

Butorphanol may cause side effects in some animals, as indicated in the TAP report. However, the ability to use this drug as an anesthetic in cases of emergency surgery on livestock outweighs concerns raised by these side effects. Butorphanol use will be limited to licensed practitioners who should be aware of the potential effects on livestock.

The most common form is butorphanol tartrate, which is the primary component of the injectable solution, Torbugesic®. Veterinarians often use Torbugesic as the injectable form of butorphanol tartrate, in combination with other drugs for sedation and anesthesia of animals prior to surgery. Approval of these other drugs, such as acepromazine and zylazine, for acceptance for the National List would need to occur independently of acceptance of butorphanol.

Little information is available on withdrawal period after administration of butorphanol to livestock. Withdrawal period in livestock used for meat or milk is an important consideration. The Northeast Organic Farming Association allows the use of anesthetics in livestock with a 5 day withholding period. The International Federation of Organic Agriculture Movements sets a standard for the withholding period of at least double the legal period for use of conventional veterinary medicines. If such a limit has not been

established for butorphanol, then its acceptance for the National List should be in accordance with other anesthetics on the List. In the treated animal, orally administered butorphanol is absorbed in the gut and distributed in the tissues, with the greatest levels in the liver, kidney and intestine. Butorphanol is metabolized in the liver and excreted as harmless metabolites of the drug. Metabolites are excreted by the kidney in urine and from the liver into the bile and eliminated in the feces. Metabolites of the drug can cross the placenta and pass into the mammary gland and into milk. Butorphanol administered intravenously is quickly metabolized and cleared from the bloodstream. This type of information should be used in establishing withdrawal periods for use of butorphanol in organic livestock production.

Reviewer 2 Conclusions and Recommendations:

Surgical procedures for livestock should be carried out only when there is no other justifiable alternative. Welfare of the animal is of primary concern in cases of surgical procedures. Anesthesia is important for relieving the animal's discomfort and pain during veterinary surgery. The petition for inclusion of butorphanol on the National List is for use as a livestock medical treatment, specifically as a synthetic narcotic for surgical procedures. As a synthetic material, butorphanol should be acceptable for inclusion on the National List provided that it is used according to all the regulations and meets all FDA requirements. If used responsibly, there should be no harm to the system of sustainable agriculture.

Limitations to acceptance of butorphanol use:

- Use of butorphanol should be limited to a licensed practitioner in accordance with FDA and DEA regulations for this controlled substance.
- Use should follow all indicated dosages.
- Withholding period after butorphanol use should be established.

Reviewer 3: *[PhD, Chemistry. Associate Professor, Chemistry and Biochemistry. Southern U.S.]*

Comments on Database

The following information needs to be corrected or added to the database:
No additional information is required.

The Technical Advisory Panel's review of butorphanol, its chemistry and applications is adequate to understand how the compound would be useful in livestock production.

Observations/OFPA Criteria

Butorphanol is a synthetic opiate agonist that provides effective pain relief to animals during emergency surgical procedures. There is no recognized benefit to chronic administration of this compound, and it is not administered as such. Also, there is no observed persistence of this compound or its metabolites that would impact on consumers. As a controlled substance, it can only be administered by a licensed veterinary practitioner under closely-monitored conditions. These restrictions are professionally and legally imposed and should continue to apply. No special restrictions need apply for organic food production certification or compliance. I see no conflict with the Federal Organic Foods Production Act of 1990, specifically part 6509, whatsoever.

Reviewer 3 Conclusions and Recommendations:

It is my recommendation that this compound and medicant be sanctioned for use, as proscribed by judicious, professional medical practice and compliance with federal law as a controlled substance, under the Federal Organic Foods Production Act of 1990.

TAP Conclusion

Of the three reviewers, one reviewer supported the use of butorphanol without restriction, while the other two supported restricted use. All agreed that the material is synthetic. All emphasized the maintenance of already-existing regulations on the drug, and one reviewer specifically mentioned enforcement of a withholding period.