Oxytocin

Livestock

Identification of Petitioned Substance

Chemical Names:
Oxytocin

CAS Numbers:
50-56-6

Other Names:
alpha-hypophamine
endopituitrina
oxtocin
pit

Other Codes:
X1026214-5 (ACX number)
QH01BB02 (ATC code; international registry)

Trade Names:
Intertocine-S (oxytocin-S)
Pitocin, Syntocinon, Uteracon (human forms)

Characterization of Petitioned Substance

Composition of the Substance:
Oxytocin is a peptide[1] hormone composed of nine amino acids (a nonapeptide) in the following sequence: cysteine, tyrosine, isoleucine, glutamine, asparagines, cysteine, praline, leucine, and glycine. It is produced primarily in two discrete locations in the brains of all male and female mammals and plays an important role in milk letdown, the contraction of the smooth uterine muscles during the birthing process, and various maternal behaviors (EMEA 2001, EPA 2005). Oxytocin was the first peptide hormone to be synthesized in its biologically active form—along with the related antidiuretic hormone (ADH), or vasopressin—by the biochemist Vincent du Vigneaud in 1953 for which he received the Nobel Prize for Chemistry in 1955 (Gimpl and Fahrenholz 2001). Synthetic oxytocin has since become widely used in veterinary and human obstetric practice and is identical in structure ($C_{44}H_{68}N_{12}O_{12}S_2$)[2] (Chemfinder 2005) to the naturally occurring hormone.

Properties of the Substance:
Oxytocin is a clear, colorless liquid that is soluble in butanol (USDA/NOSB 1995) and water (APP 2005). It is chemically stable at normal temperature and pressure (APP 2005).

Specific Uses of the Substance:
The name "oxytocin" means "rapid birth," due to its ability to contract the pregnant uterus (Gimpl and Fahrenholz 2001). The primary general veterinary uses of oxytocin include the following obstetrical uses: stimulate uterine contraction to facilitate parturition (animal birth); promote the return of the post-parturient uterus to pre-pregnancy conditions and aid the passage of retained placentae and the removal of detritus; and help control post partum hemorrhage. Oxytocin is also used to promote milk letdown in cases of agalactia (lack of milk) and to facilitate treatment of mastitis (infection or inflammation of the mammary glands) in cows (EMEA 2001, Intervet UK 2003).

Current U.S. Food and Drug Administration regulations (FDA 1999) allow for obstetric use of injected (intravenous, subcutaneous, or intramuscular) oxytocin in several livestock (e.g., 5 mL in cows) and domestic animal species (e.g., 0.25-1.25 mL in dogs) by or on the order of a licensed veterinarian. Similarly, use of injected (intravenous route is recommended) oxytocin is also allowed to assist in milk letdown in

[1] A peptide is one of a family of molecules formed from the linking various amino acids in a specific order.
[2] Although the amino acid sequence of oxytocin is established in the literature, the hormone's molecular structure is reported to be $C_{43}H_{66}N_{12}O_{12}S_2$ (USDA/NOSB 1995, PubChem 2005).

cows (0.5-1.0 mL) and sows (0.25-1.0 mL). Each milliliter of injected oxytocin contains 20 U.S.P. units of oxytocin.

Oxytocin is currently included on the National List of Allowed and Prohibited Substances as a synthetic substance allowed for use in organic livestock production (7 CFR §205.603). Use of oxytocin is limited to "use in postparturition therapeutic applications." These uses are not specifically defined, but presumably do not include prolonged use to promote milk production.

Approved Legal Uses of the Substance:
Federal law restricts oxytocin to intravenous, subcutaneous, or intramuscular use under aseptic conditions in several livestock and other animal species by or on the order of a licensed veterinarian (FDA 1999).

Action of the Substance:
Naturally produced (i.e., endogenous) oxytocin originates primarily in two distinct groups of magnocellular neurosecretory cells in the hypothalamus (brain) of mammals (EMEA 2001). The first group of cells secretes oxytocin to the posterior lobe of the pituitary, which is an endocrine gland located at the base of the brain. From the pituitary, oxytocin is released into the bloodstream. Natural or synthetic oxytocin in the bloodstream exerts the well-known physiological and pharmacological effects on smooth muscle fibers of female reproductive organs and tissues resulting in rhythmic and forceful uterine contraction and milk letdown in response to a variety of nervous stimuli such as parturition and suckling, respectively. The second group of oxytocin-producing cells provides oxytocin directly to specific brain areas that are known to mediate complex maternal and other social behaviors. See Gimpl and Fahrenholz (2001) for a comprehensive review of the structure, function, and regulation of the oxytocin receptor system in humans and animals (especially experimental rats).

Status

International
Oxytocin is not specifically listed for the petitioned use or other uses in the following international organic standards:

- Canadian General Standards Board
- CODEX Alimentarius Commission
- European Economic Community (EEC) Council Regulation 2092/91
- International Federation of Organic Agriculture Movements
- Japan Agricultural Standard for Organic Production

The Canadian British Columbia Certified Organic Production Operation Policies and Management Standards (COABC 2005) allows the use of oxytocin for the treatment of mastitis or to encourage milk let down in heifers during the first few days of lactation, on the recommendation of a veterinarian. It is not permitted for long-term or regular use. Milk produced from treated animals must be withdrawn from the production stream for two times the label recommendation time if one exists or for ten days, whichever is greater, from the date of the last treatment.

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

Evaluation Question #1: Is the petitioned substance formulated or manufactured by a chemical process? (From 7 U.S.C. § 6502 (21))

Yes. Oxytocin is chemically manufactured as a both a veterinary and medical synthetic hormone. In brief, oxytocin's peptide synthesis goes through multiple steps and involves a series of condensation reactions using various solvents (e.g., triethylamine, ether) to form amide bonds (USDA/NOSB 1995). A more detailed discussion of the chemical synthesis of oxytocin was not available.

Biologically active oxytocin exists in a cyclic configuration formed by oxidation of two thiol groups to form a disulfide bond between the cysteine and asparagines amino acids (see Figure 1). Other molecular configurations (e.g., non-cyclic) also may exist.

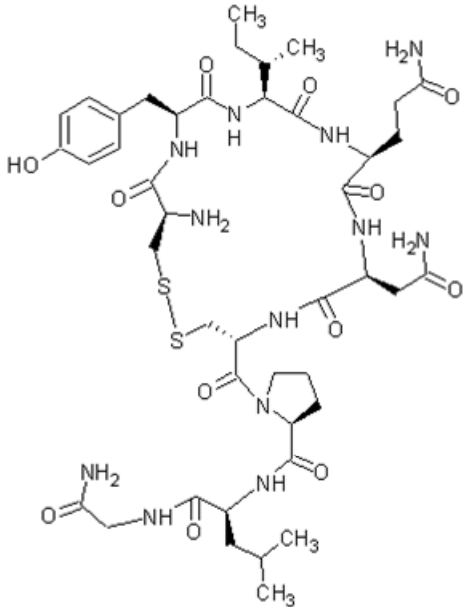

Figure 1. Chemical Structure of Oxytocin

<u>Evaluation Question #2:</u> Is the petitioned substance formulated or manufactured by a process that chemically changes the substance extracted from naturally occurring plant, animal, or mineral sources? (From 7 U.S.C. § 6502 (21).)

No. Although oxytocin is a naturally biosynthesized hormone that is produced from amino acids by all mammals, primarily in the brain, it is not concentrated or collected for external veterinary use (EMEA 2001).

<u>Evaluation Question #3:</u> Is the petitioned substance created by naturally occurring biological processes? (From 7 U.S.C. § 6502 (21).)

No, veterinary oxytocin is chemically synthesized (see Evaluation Question # 1). However, several researchers of the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry (Moscow, Russia) have recently developed an *in vitro* method using the plasmid DNA containing the gene of the recombinant protein for oxytocin to produce purified oxytocin from an overexpressed hybrid protein in *Escherichia coli* (Esipov et al. 2003). Based on their findings, the authors suggested that expanded development and use of their method would allow high (commercial) yields of oxytocin in the future.

<u>Evaluation Question #4:</u> Is there environmental contamination during the petitioned substance's manufacture, use, misuse, or disposal? (From 7 U.S.C. § 6518 (m) (3).)

No information was available on environmental contamination resulting from the manufacture or deliberate disposal of manufactured oxytocin, and there was very limited information on environmental contamination resulting from the veterinary use of oxytocin (DEPA 2002). In general, the predominant pathway of environmental release of veterinary medicines in the terrestrial environment is by amendment of arable soil with manure from treated animals. Because oxytocin is soluble in water (i.e., hydrophilic), it will be dissolved in the aqueous fraction of the manure and may lead to run-off in cases of precipitation.

However, because oxytocin is used in small doses on a case-by-case basis and only by or under the direction of a veterinarian in organic livestock production (EMEA 2001), it is unlikely to reach significant concentrations in the environment (agro-ecosystem) through normal use.

An environmental assessment of veterinary medical products in Denmark (DEPA 2002) determined that no information was available on the fate of veterinary medicinal products during storage of manure. Using a "realistic worst case" scenario (i.e., degradation during storage was not considered), the DEPA report estimated that soil amended with manure from pigs or cattle administered oxytocin may contain 0.01-0.05 µg/kg (dry weight) of oxytocin. In cases of direct deposition of manure on the soil with no subsequent tilling, the concentration of excreted oxytocin could be higher locally. However, no assessment or discussion was provided for the concentration of oxytocin breakdown products in amended soils or of the ecotoxicity of oxytocin or its breakdown products.

Evaluation Question #5: Is the petitioned substance harmful to the environment? (From 7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i).)

None of the readily available information sources included a detailed evaluation of whether or not oxytocin excreted from treated animals is harmful to the environment. However, a notice in 2004 by the U.S. Food and Drug Administration's Center for Veterinary Medicine (CVM) pursuant to an abbreviated new animal drug application (ANADA) concluded that environmental impacts from oxytocin use are unlikely. In particular, CVM provided notice that it approved an ANADA filed by Cross Vetpharm Group, Ltd (Broomhill, Ireland) for the veterinary prescription use of oxytocin injectable solution in ewes, sows, cows, and horses. Notably, CVM determined under 21 CFR 25.33(a)(1) that "this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required" (FDA 2004).

The Danish Environmental Protection Agency (2002) environmental assessment of veterinary medical products (see Evaluation Question #4) concluded that it is not possible to determine from the data available whether the current normal veterinary use of hormones (including oxytocin) may have adverse effects on the environment.

In general, the acute toxicity of oxytocin is considered low (EMEA 2001). The lethal dose (LD_{50}) of oxytocin has been determined by the oral route of administration in rats (> 20.5 mg/kg) and mice (> 514 mg/kg) (APP 2005). Its LD_{50} in rats via intravenous administration is much lower and has been reported in the literature to range from > 2.275 mg/kg (DF&S 2004) to 5.8 mg/kg (EMEA 2001). Veterinary oxytocin is not available in oral form because it is destroyed in the stomach and intestines of mammals (DF&S 2004). More specifically, the nonapetide is degraded into biologically inactive smaller peptides and amino acids by enzymes of the gastrointestinal tract (EMEA 2001).

Evaluation Question #6: Is there potential for the petitioned substance to cause detrimental chemical interaction with other substances used in organic crop or livestock production? (From 7 U.S.C. § 6518 (m) (1).)

No information was available to assess whether administered and excreted oxytocin or its byproducts can react detrimentally with other substances used in livestock or organic crop production. However, because properly administered (injected) oxytocin is used in small doses over short periods of time in postparturition therapeutic applications, it is unlikely to reach the greater agro-ecosystem in significant amounts and thus is unlikely to be available to chemically interact with other substances (see Evaluation Questions #4 and #5).

Evaluation Question #7: Are there adverse biological or chemical interactions in the agro-ecosystem by using the petitioned substance? (From 7 U.S.C. § 6518 (m) (5).)

No information was available to assess whether administered and excreted oxytocin or its byproducts can have adverse biological or chemical reactions in the agro-ecosystem. However, because oxytocin is only used in small injected doses over short periods of time in postparturition therapeutic applications in organic livestock production, it is unlikely to reach the agro-ecosystem in sufficient concentrations to be of concern (see Evaluation Questions #4, #5, and #6).

Evaluation Question #8: Are there detrimental physiological effects on soil organisms, crops, or livestock by using the petitioned substance? (From 7 U.S.C. § 6518 (m) (5).)

Two of three veterinarians that submitted TAP Reviews for the 1995 USDA/NOSB file checklist for oxytocin reported that regular use of oxytocin injections to increase dairy milk production can lead to both desensitization of cows to future oxytocin injections and an addiction to oxytocin whereby further injections are required for milk letdown, respectively. In this regard, a recent article by Bruckmaier (2003) found that chronic administration of oxytocin leads to reduced milk ejection in dairy cows after oxytocin treatments are suspended. Oxytocin is currently listed only for use in "post-parturition therapeutic applications," which presumably does not include prolonged use to increase dairy milk production.

Although oxytocin is a potent hormone influencing parturition, lactation, and social behavior when administered intravenously, subcutaneously, or intramuscularly (Gimpl and Fahrenholz 2001), accidental or intentional oral consumption of trace amounts in contaminated soil or water is unlikely to create unacceptable changes in behavior, fertility, metabolism, or mortality of livestock (USDA/NOSB 1995) (see Evaluation Questions #4 and #5). Furthermore, the 2002 DEPA report on veterinary medical products in the environment concluded that it is not possible to determine whether normal veterinary use of hormones (including oxytocin) may have adverse effects on the environment.

Evaluation Question #9: Is there a toxic or other adverse action of the petitioned substance or its breakdown products? (From 7 U.S.C. § 6518 (m) (2).)

Veterinary use of oxytocin is associated with a number of potential adverse side effects and has several potential side effects, including (DF&S 2004): uterine cramping and discomfort; uterine rupture, fetal injury, or fetal death if used when the fetuses are malpositioned or too large for a natural birth; allergic reactions (e.g., facial swelling, diarrhea, vomiting, shock, seizures, coma). Use of oxytocin is not recommended for animals that are hypersensitive (allergic) to it; animals with dystocia (difficulty giving birth) due to malposition of the fetus, small pelvis in the mother, large fetal size, or when a cesarean section is otherwise warranted; animals with pyometra (infection in the uterus) (DF&S 2005, Intervet 2005). Excessive doses of oxytocin may delay parturition by producing uncoordinated uterine contractions, which interfere with the progress of the fetus, especially in multiple pregnancies. As noted in Evaluation Question #8 above, there are anecdotal veterinarian reports of regular use of oxytocin injections in dairy cows to increase milk production leading to desensitization or addiction to future injections for milk letdown. However, these reactions are documented in intentionally dosed animals—not in animals secondarily exposed through a dietary and/or environmental pathway.

No adverse effects have been observed in newborn animals when oxytocin (Intertocin-S) is used at the recommended doses (Intervet 2005).

Evaluation Question #10: Is there undesirable persistence or concentration of the petitioned substance or its breakdown products in the environment? (From 7 U.S.C. § 6518 (m) (2).)

No information was available to assess whether administered and excreted oxytocin or its byproducts can have undesirable persistence or concentration in the environment. The Danish environmental assessment of veterinary medicinal products (DEPA 2002) estimated that soils amended with manure from oxytocin-treated livestock would contain detectable levels of oxytocin but no assessment or discussion was provided

for the concentration of oxytocin byproducts or of the ecotoxicity of oxytocin or its byproducts (see Evaluation Questions #4 and #5).

Evaluation Question #11: Is there any harmful effect on human health by using the petitioned substance? (From 7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4).)

No information was available to assess whether veterinary use of oxytocin in organic livestock production and its subsequent excretion in the agro-environment can result in harmful human health effects in those exposed to it or its breakdown products in contaminated milk, soil, groundwater, or treated drinking water. For example, oxytocin consumed by humans in contaminated milk or drinking water would likely be destroyed in their stomach and intestines (see Evaluation Question #5). Thus, given its limited and veterinarian-prescribed use in small injected doses, it is unlikely that humans exposed to excreted oxytocin in contaminated soil or water could result in adverse health effects.

Although intentional medical use of oxytocin in women has taken place for decades, its use is associated with a number of potential adverse side effects and has several contraindications (Multum 2004). Synthetic oxytocin is most commonly used in a clinical setting to induce labor, strengthen labor contractions during childbirth, control vaginal bleeding after childbirth, or to induce an abortion. Particular care should be taken to avoid the accidental self-injection of oxytocin into women in late pregnancy (Intervet UK 2003). There are no known indications for the medical use of oxytocin in the first or second trimester of pregnancy other than in relation to spontaneous or induced abortion (Multum 2004). Mild side effects (e.g., nausea or vomiting) associated with medicinal use of oxytocin in women are uncommon; some serious side effects (e.g., allergic reactions, excessive vaginal bleeding) have been reported but are much less likely to occur. Based on the wide experience with this drug and its properties, it would not be expected to present a risk of harm to the baby when used as indicated under proper medical supervision (Multum 2004).

Evaluation Question #12: Is there a wholly natural product that could be substituted for the petitioned substance? (From 7 U.S.C. § 6517 (c) (1) (A) (ii).)

No. As noted previously, naturally biosynthesized oxytocin is produced in all mammals, including livestock, but it is not extracted and sold commercially. No information was available regarding any other natural products that could be used instead of oxytocin (USDA/NOSB 1995).

Evaluation Question #13: Are there other already allowed substances that could be substituted for the petitioned substance? (From 7 U.S.C. § 6518 (m) (6).)

No. Oxytocin is the only synthetic hormone currently on the National List (USDA 2003) that can be used in postparturition therapeutic applications.

Evaluation Question #14: Are there alternative practices that would make the use of the petitioned substance unnecessary? (From 7 U.S.C. § 6518 (m) (6).)

All three veterinarians that submitted TAP Reviews for the 1995 USDA/NOSB file checklist for oxytocin reported that there are no well explored or accepted alternative practices or substances to substitute injection of synthetic oxytocin in "certain health cases" in livestock production. Presumably, the three veterinarians were referring to a lack of accepted alternatives to the obstetric veterinary uses of oxytocin (e.g., to facilitate parturition, help control post-partum hemorrhage).

One of the veterinarians stated that homeopathic herbs or acupuncture may alleviate some symptoms and conditions associated with parturition and milk production that might otherwise be treated through oxytocin injection. For example, injected oxytocin is used to treat mastitis (infection or inflammation of the mammary glands) for which there are alternative practices such as those suggested by Northeast Organic Dairy Producers Alliance (NODPA 2005). These include use of the following homeopathic practices, herbal/plant based products, and dairy cow immune system supports: (1) checking trace mineral levels of zinc, iodine, selenium, and copper; (2) use of colostrum whey, (3) use of anti-oxidant vitamins (C, E, A;

both injectable and feed-grade); feeding dairy cows mash/gruel of vinegar, molasses, bran, and beet pulp; (4) use of herbal extracts (e.g., cayenne, ginger, mint); and (5) massaging the udder with "hot" liniment (e.g., camphor, peppermint, capsicum, etc).

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