Executive summary
Furosemide was petitioned as a synthetic substance allowed for use in organic livestock production. The exact mode of action of furosemide has not been clearly defined; in contrast to ethacrynic acid, it does not bind sulfhydryl groups of renal cellular proteins. Furosemide inhibits the reabsorption of electrolytes in the ascending limb of the loop of Henle. The drug also decreases reabsorption of sodium and chloride and increases potassium excretion in the distal renal tubule and exerts a direct effect on electrolyte transport at the proximal tubule. It is extremely difficult to overdose with this medication. Toxic doses reported are over 100 times a typical oral dose of medication. It is important to realize that in the treatment of heart failure (this drug’s primary use), a crisis can arise at any time. Often giving an extra dose of oral medication can be a life saving procedure.

Furosemide is not officially listed anywhere in the NOP final rule. As in section 205.600 of the NOP final rule, “any synthetic substance used as a processing aid or adjuvant will be evaluated against the following criteria: (2) the substance’s manufacture, used and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling.” Furosemide is not explicitly listed in section 205.603 as a synthetic substance, allowed for use in organic livestock production nor is it listed in section 205.604 as a prohibited substance.

Summary of TAP Reviewer’s Analyses

<table>
<thead>
<tr>
<th>Synthetic/ Nonsynthetic</th>
<th>Allow without restrictions?</th>
<th>Allow only with restrictions? (See Reviewers’ comments for restrictions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic (3)</td>
<td>Yes (0)</td>
<td>Yes (2)</td>
</tr>
<tr>
<td>Nonsynthetic (0)</td>
<td>No (3)</td>
<td>No (1)</td>
</tr>
</tbody>
</table>

Identification
Chemical names: Furosemide
CASRN: 54-31-9
Molecular Formula: C_{12}H_{11}Cl-N_2O_5S
Molecular Weight: 330.77

Other Names: 5-(Aminosulfonyl)-4-chloro-2-[(2-furanyl)methyl]-amino]-benzoic acid, Aluzine, Aquamide, Aquasin, Arasemide, Discoid, Disal, Diural, Diuresal, Diurolasa, Dryptal, Durafurid, Errolon, Franyl, Frusetic, Furetic, Furix, Furo-basan, Fur-O-ImS, Furo-Puren, Furose, Fusid, Hydrex,

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.
Hydro-rapid, Impugan, Lasiletten, Lasilix Lasix, Laxur, Min-I-Jet Frusemide, Molarorin, Neo-Renal, Nicorol, Novosemide Odemase, Oedemex, Promedes, Puresis, Seguril, Sigasalur, SK-Furosemide Sulfamoylanthranilic acid, 4-chloro-N-furfuryl-5, Uremide, Urex, Urex-M, Uritol  

The structural formula is as follows:

![Structural formula of furosemide](image)

**Characterization**

**Composition:**
"LASIX® is a diuretic which is an anthranilic acid derivative. LASIX tablets for oral administration contain furosemide as the active ingredient and the following inactive ingredients: lactose USP, magnesium stearate NF, starch NF, talc USP, and colloidal silicon dioxide NF. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. LASIX is available as white tablets for oral administration in dosage strengths of 20, 40 and 80 mg. Furosemide is a white to off-white odorless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids.”

**Properties:**

**Origin of the substance:** Synthetic

**Color:** White or slightly yellow.

**State/form:** Solid-crystals
Solid-powder

**Description:** Odorless.

Practically insoluble in water; very slightly soluble in chloroform; soluble in alcohol; slightly soluble in ether; freely soluble in acetone; dimethyl formamide; methyl alcohol and solutions of alkali hydroxides.

pKₐ 3.9 (20°C)

**Shelf-life of the substance:** No data available.

**Storage conditions:** Protect from light
Store at a temperature between 15 to 30°C.
SPECIFIC GRAVITY: Not available

DENSITY: Not available

MP (DEG C): 206 C (decomposes) [295]

*BP (DEG C): Not available

*SOLUBILITIES:
   WATER : <1 mg/mL @ 23 C (RAD)
   DMSO : >=100 mg/mL @ 23 C (RAD)

95% ETHANOL : 10-50 mg/mL @ 23 C (RAD)

METHANOL : Soluble [031,159]

ACETONE : 50-100 mg/mL @ 23 C (RAD)

TOLUENE : Not available

OTHER SOLVENTS:
   Dimethylformamide: Freely soluble [159,295]
   Solutions of alkali hydroxides: Freely soluble [159,295,365]
   Chloroform: Very slightly soluble [159,365,455]
   Ether: Slightly soluble [159,365]
   Aqueous solutions above pH 8.0: Soluble [031]

VOLATILITY:
   Vapor pressure: Not available
   Vapor density : Not available

FLAMMABILITY (FLASH POINT):
   Flash point data for this chemical are not available; however, it is probably combustible. Fires involving this material can be controlled with a carbon dioxide, dry chemical or Halon extinguisher.

UEL: Not available        LEL: Not available

REACTIVITY:
   This chemical is incompatible with strong oxidizing agents [269].

STABILITY:
   This chemical is light sensitive and hygroscopic [269,275]. It is also air sensitive. Solutions of this chemical in water, DMSO, 95% ethanol or acetone should be stable for 24 hours under normal lab conditions (RAD). In solution, this chemical may undergo hydrolysis at sufficiently low pH. The pH of aqueous solutions should be maintained in the basic range to prevent hydrolysis. Alcohol has been shown to improve the stability of this compound.  

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Specific Uses:
“Furosemide is a diuretic. It has been used extensively since 1964 in the treatment of oedema and hypertension.” 7 “This medicine is used to rid the body of excess fluid (salt and water). Patients who frequently have this problem are ones with weakened hearts (congestive heart failure), poor kidney function, or poor liver function. It can be used to reduce blood pressure in these patients.” 8

- Clinical Uses:
  - Major uses:
    - acute pulmonary edema
    - acute hypercalcemia
    - management of edema
  - Other uses:
    - Reduction of Intracranial Pressure
    - hyperkalemia:
      - loop diuretics increase potassium excretion
      - effect increased by concurrent administration of NaCl and water.
    - acute renal failure:
      - may increase rate of urine flow and increase potassium excretion.
      - may convert oligouric to non-oligouric failure {easier clinical management}
      - renal failure duration -- not affected
    - anion overload:
      - bromide, chloride, iodide: all reabsorbed by the thick ascending loop:
      - systemic toxicity may be reduced by decreasing reabsorption
      - concurrent administration of sodium chloride and fluid is required to prevent volume depletion 9

Action:
“The pharmacologic effects of furosemide are similar to those of ethacrynic acid. The exact mode of action of furosemide has not been clearly defined; in contrast to ethacrynic acid, it does not bind sulfhydryl groups of renal cellular proteins. Furosemide inhibits the reabsorption of electrolytes in the ascending limb of the loop of Henle. The drug also decreases reabsorption of sodium and chloride and increases potassium excretion in the distal renal tubule and exerts a direct effect on electrolyte transport at the proximal tubule. Furosemide does not inhibit carbonic anhydrase and is not an aldosterone antagonist.” 10 “Furosemide inhibits the coupled Na+/K+/2Cl- transport system in the luminal membrane of the thick ascending limb of the loop of Henle. Thus the loop diuretics reduce the reabsorption of NaCl and also diminish the normal lumen-positive potential that derives from K+ recycling.” 11

- Mechanism of action:
  - inhibition of NaCl reabsorption in the thick ascending limb of the loop of Henle
    - inhibit the Na/K/2Cl transport system in the luminal membrane
      1. reduction in sodium chloride reabsorption
      2. decreases normal lumen-positive potential (secondary to potassium recycling)
      3. Positive lumen potential: drives divalent cationic reabsorption (calcium magnesium)
      4. Therefore, loop diuretics increase magnesium and calcium excretion.

1 Directly referenced from http://193.51.164.11/htdocs/Monographs/Vol50/13-Furosemide.htm
2 Directly referenced from http://www.ivillagehealth.com/library/onemed/content/0,7064,241012_246232,00.html#Mechanism
3 Directly referenced from http://www.pharmacology2000.com/Central/General_Anesthesia/loop1.htm#Major%20uses
4 Directly referenced from http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAzhs4Ob:1
5 Directly referenced from http://lysine.pharm.utah.edu/netpharm/netpharm_00/druglist/furosemide.htm
hypocalcemia does not usually develop because calcium is reabsorbed in the distal convoluted tubule.
• {in circumstances that result in hypercalcemia, calcium excretion can be enhanced by administration of loop diuretics with saline infusion}
  o Since a significant percentage of filtered NaCl is absorbed by the thick ascending limb of loop of Henle, diuretics acting at this site are highly effective

BRAND NAME: LASIX, DISAL
Available in oral solution (8 or 10 mg/ml), 12.5 mg tablets, 20 mg tablets, 40 mg tablet, 50 mg tablets, 80 mg tablets (and injectable)

“Store tablets in a tight, light-resistant container at room temperature.
Store liquid (solution) in a tight, light-resistant container at room temperature. Do not freeze. Furosemide acts on the kidney to remove more water and salt.”

“Loop diuretics inhibit reabsorption of NaCl and KCl by inhibiting the Na+-K+-2Cl- symport in the luminal membrane of the thick ascending limb (TAL) of loop of Henle. As TAL is responsible for the reabsorption of 35% of filtered sodium, and there are no significant downstream compensatory reabsorption mechanisms, loop diuretics are highly efficacious and are thus called high ceiling diuretics. As the Na+-K+-2Cl- symport and sodium pump together generate a positive lumen potential that drives the reabsorption of Ca++ and Mg++, inhibitors of the Na+-K+-2Cl- symport also inhibit reabsorption of Ca++ and Mg++. By unknown mechanisms (possibly prostaglandin-mediated), loop diuretics also have direct effects on vasculature including increase in renal blood flow, and increase in systemic venous capacitance.”

How Supplied: Injection: 10 mg/mL; Solution: 10 mg/mL, 40 mg/5 mL; Tablet: 20 mg, 40 mg, 80 mg

Dosage
• Oral Solution, Tablets Edema.
  Adults, initial: 20-80 mg/day as a single dose. For resistant cases, dosage can be increased by 20-40 mg q 6-8 hr until desired diuretic response is attained. Maximum daily dose should not exceed 600 mg.
  Pediatric, initial: 2 mg/kg as a single dose; then, dose can be increased by 1-2 mg/kg q 6-8 hr until desired response is attained (up to 5 mg/kg may be required in children with nephrotic syndrome; maximum dose should not exceed 6 mg/kg). A dose range of 0.5-2 mg/kg b.i.d. has also been recommended.
  Hypertension.
  Adults, initial: 40 mg b.i.d. Adjust dosage depending on response.
  CHF and chronic renal failure.
  Adults: 2-2.5 g/day.
  Antihypercalcemic.
  Adults: 120 mg/day in one to three doses.
  • IV, IM Edema.
  Adults, initial: 20-40 mg; if response inadequate after 2 hr, increase dose in 20-mg increments. Pediatric, initial: 1 mg/kg given slowly; if response inadequate after 2 hr, increase dose by 1 mg/kg. Doses greater than 6 mg/kg should not be given.
  Antihypercalcemic.
  Adults: 80-100 mg for severe cases; dose may be repeated q 1-2 hr if needed.
  • IV Acute pulmonary edema.
  Adults: 40 mg slowly over 1-2 min; if response inadequate after 1 hr, give 80 mg slowly over 1-2 min. Concomitant oxygen and digitalis may be used.

12 Directly referenced from http://www.pharmacology2000.com/Central/General_Anesthesia/loop1.htm#Major%20uses
13 Directly referenced from http://www.vin.com/PetCare/Articles/VetHospital/M00585.htm
14 Directly referenced from http://www.ivillagehealth.com/library/onemed/content/0,7064,241012_246232,00.html#Mechanism
15 Directly referenced from http://www.uic.edu/classes/pcol/pcol425/restricted/Du/diuretics.PDF
CHF, chronic renal failure.

**Adults:** 2-2.5 g/day. For IV bolus injections, the maximum should not exceed 1 g/day given over 30 min.

**Hypertensive crisis, normal renal function.**

**Adults:** 40-80 mg.

**Hypertensive crisis with pulmonary edema or acute renal failure.**

**Adults:** 100-200 mg.  

**Combinations:**

Furosemide has some renal vasodilator effect; renal vascular resistance decreases and renal blood flow increases following administration of the drug. A temporary but substantial increase in glomerular filtration rate, as well as decreased peripheral vascular resistance and increased peripheral venous capacitance, has been reported following IV administration of furosemide in patients with congestive heart failure associated with acute myocardial infarction. The renal and peripheral vascular effects may contribute toward the beneficial effects of the drug in these patients, as a decrease in left ventricular filling pressure occurs before the onset of substantial diuresis. In addition, IV administration of furosemide in patients with congestive heart failure results in a decrease in plasma volume, increased hematocrit, and a fall in mean arterial pressure associated with increased cardiac output and decreased peripheral resistance. When large doses of furosemide are administered to patients with chronic renal insufficiency, glomerular filtration rate may be increased temporarily. A fall in renal blood flow and glomerular filtration rate may occur if excessive drug induced diuresis results in a reduction in plasma volume.


**Interactions:**

CEPHALORIDINE NEPHROTOXICITY IS ENHANCED BY CONCURRENT FUROSEMIDE ADMIN.

...FUROSEMIDE ... MAY CAUSE HYPOKALEMIA WHICH WILL ENHANCE CARDIOTOXIC EFFECTS OF DIGITALIS GLYCOSIDES.

CONCURRENT ADMIN OF AGENTS SUCH AS AMINOGLYCOSIDE ANTIBIOTICS ... THAT HAVE BEEN ASSOC WITH COCHLEAR DAMAGE SHOULD BE USED WITH CAUTION.

DEPLETION OF POTASSIUM RESULTS IN INCREASED SENSITIVITY TO DIGITALIS AND MAY PRECIPITATE CARDIAC ARRHYTHMIAS IN PATIENTS WITH MYOCARDIAL ISCHEMIA. FUROSEMIDE SHOULD BE ADMINISTERED WITH CAUTION TO PATIENTS RECEIVING POTASSIUM-DEPLETING COMPD SUCH AS CORTICOSTEROIDS.
[american society of hospital pharmacists. data supplied on contract from american hospital formulary service and other current ASHP sources. 1970]**PEER REVIEWED**

SINCE SULFONAMIDE DIURETICS ... DECREASE ARTERIAL RESPONSIVENESS TO PRESSOR AMINES AND ... ENHANCE EFFECT OF TUBOCURARINE, CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING CURARE OR ITS DERIVATIVES TO PATIENTS /RECEIVING FUROSEMIDE/.
[american society of hospital pharmacists. data supplied on contract from american hospital formulary service and other current ASHP sources. 1970]**PEER REVIEWED**

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FUROSEMIDE MAY POTENTIATE ACTION OF HYPOTENSIVE DRUGS IF ADMIN
CONCOMITANTLY ... FUROSEMIDE AND SALICYLATES ... HAVE COMPETITIVE RENAL
EXCRETORY SITES AND ... PATIENTS RECEIVING DRUGS CONCOMITANTLY MAY
EXPERIENCE SALICYLATE TOXICITY AT LOWER DOSAGE THAN USUAL.
[American Society of Hospital Pharmacists. Data supplied on contract from American Hospital Formulary
Service and other current ASHP sources. 1970]**PEER REVIEWED**

CONCLUDED THAT INHIBITORY EFFECT OF SINGLE DOSE OF FUROSEMIDE ON DIGOXIN
EXCRETION TOO SHORT FOR CLINICAL SIGNIFICANCE; MAY BE POSSIBLE TO ELEVATE
SERUM DIGOXIN CONCN IF FUROSEMIDE GIVEN MORE FREQUENTLY. WHEN 6 HEALTHY
SUBJECTS RECEIVING 0.006 MG/KG DIGOXIN IV WERE GIVEN ORAL FUROSEMIDE, I
CLEARANCE DURING DIURETIC PHASE & EXCRETION AFTER DIURESIS DECR MUCH. AVG
SERUM HALF-LIFE PROLONGED FROM 37 HR IN CONTROL PERIOD TO 86 HR IN
FUROSEMIDE PERIOD.
[TSUTSUMI E ET AL; J CLIN PHARMACOL 19 (APR): 200-4 (1979)]**PEER REVIEWED**

Diflunisal decreases the hyperuricemic effect of furosemide and hydrochlorothiazide. It has no effect on
diuretic activity of furosemide but significantly increases levels of hydrochlorothiazide.
Association, 1991.,p. 1706]**PEER REVIEWED**

Concomitant administration of furosemide and most other diuretics results in enhanced effects, and
furosemide should be administered in reduced dosage when the drug is added to an existing diuretic
regimen. Spironolactone, triamterene, or amiloride hydrochloride may reduce the potassium loss resulting
from furosemide therapy; this effect has been used to therapeutic advantage.
American Society of Hospital Pharmacists, Inc., 1993 (Plus Supplements, 1993). 1632]**PEER
REVIEWED**

In patients receiving cardiac glycosides, electrolyte disturbances produced by furosemide (principally
hypokalemia but also hypomagnesemia) predispose the patient to glycoside toxicity. Possibly fatal cardiac
arrhythmias may result.
American Society of Hospital Pharmacists, Inc., 1993 (Plus Supplements, 1993). 1632]**PEER
REVIEWED**

Furosemide reportedly causes prolonged neuromuscular blockade in patients receiving nondepolarizing
neuromuscular blocking agents (eg, tubocurarine chloride, gallamine triethiodide), presumably because of
potassium depletion or decreased urinary excretion of the muscle relaxant. Furosemide may also cause
decreased arterial responsiveness to pressor amines
American Society of Hospital Pharmacists, Inc., 1993 (Plus Supplements, 1993). 1632]**PEER
REVIEWED**

Some drugs such as corticosteroids, corticotropin, and amphotericin B also cause potassium loss, and
severe potassium depletion may occur when one of these drugs is administered during furosemide therapy.
American Society of Hospital Pharmacists, Inc., 1993 (Plus Supplements, 1993). 1632]**PEER
REVIEWED**

Renal clearance of lithium is apparently decreased in patients receiving diuretics, and lithium toxicity may
result.
Administration of furosemide to diabetic patients may interfere with the hypoglycemic effect of insulin or oral antidiabetic agents, possibly as a result of hypokalemia.

The antihypertensive effect of hypotensive agents may be enhanced when given concomitantly with furosemide. This effect is usually used to therapeutic advantage; however, orthostatic hypotension may result.

In some patients, indomethacin may reduce the natriuretic and hypotensive effects of furosemide. The mechanism(s) of these interactions is uncertain but has been attributed to indomethacin induced inhibition of prostaglandin synthesis which may result in fluid retention and/or changes in vascular resistance.

Concomitant administration of furosemide and aminoglycoside antibiotics or other ototoxic drugs may result in increased incidence of ototoxicity and concomitant use of these drugs should be avoided. In addition, the possibility that IV furosemide may increase aminoglycoside toxicity by altering serum and tissue concentrations of the antibiotic should be considered. It has been proposed, but not proven, that furosemide may enhance the nephrotoxicity of neomycin.

**Status**

**Historic Use by Organic Farmers:**

“For many years the Houston Livestock Show used established pre-set weight breaks in their market animal shows: steers, lambs and barrows. There was speculation that exhibitors, in their attempt to show an animal at the top of a weight class, were using Lasix to draw an animal’s weight before show weigh-in.

In 1980 and 1981, Houston tested market hogs for Lasix. This testing program was carried out by Dr. T.D. Tanksley, the head of the Swine Production Program at Texas A&M University. A show rule was in place that animals would be disqualified if a diuretic was found in the urine. In 1981 Houston disqualified one pig.”

“The history of Lasix provides a good example of the usual route that medications take in their use by humans and pets. Lasix was introduced by Hoechst Pharmaceuticals into human health care in 1966 to control the buildup of fluids associated with heart failure and kidney and liver diseases. It also is used in people for treatment of high blood pressure. Eleven years later, Hoechst-Roussel Agri-Vet, the manufacturer’s animal health division, introduced Lasix for veterinary use. Dogs (and cats and horses) with congestive heart failure benefit from administration of Lasix.”

Lasix was also routinely used in cattle, administered by veterinarians, if there was difficulty in dispensing milk. Lasix would reduce udder edema and allow for easier milk flow.

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17 Directly referenced from http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAzba4Ob:1
18 Directly referenced from http://www.animalagriculture.org/Proceedings/1999%20NYLPES/a%20look%20at%20the%20history%20of%20residue%20avoidance.htm
19 Directly referenced from http://www.ncabrf.org/ncabr.msf/web/research/partners
20 Information was referenced from http://www.adirondackllamafarm.com/all%20about%20llamas.htm
“Furosemide is a potent diuretic that is ostensibly used in racehorses to prevent exercise-induced pulmonary hemorrhage. Field studies suggest that horses receiving furosemide may race faster than horses that do not. To determine the effect of furosemide on performance of Thoroughbreds, race records were obtained for all Thoroughbreds (n = 22,589) that raced on dirt surfaces at tracks in the United States and Canada between June 28 and July 13, 1997 in jurisdictions that allowed the use of furosemide. Multivariate ANOVA procedures and logistic regression analyses were used to determine the effect of furosemide on estimated 6-furlong race time, estimated racing speed, race earnings, and finish position. Principal component analysis was used to create orthogonal scores from multiple collinear variables for inclusion in the models. Records indicated that furosemide was administered to 16,761 (74.2%) horses. Horses that received furosemide raced faster, earned more money, and were more likely to win or finish in the top 3 positions than horses that did not. The magnitude of the effect of furosemide on estimated 6-furlong race time varied with sex, with the greatest effect in males. When comparing horses of the same sex, horses receiving furosemide had an estimated 6-furlong race time that ranged from 0.56 ± 0.04 seconds (least-squares mean ± SE) to 1.09 ± 0.07 seconds less than that for horses not receiving furosemide, a difference equivalent to 3.5 to 5.5 lengths.”

**OFPA, USDA Final Rule:**
Furosemide is not officially listed anywhere in the NOP final rule. As in section 205.600 of the NOP final rule, “any synthetic substance used as a processing aid or adjuvant will be evaluated against the following criteria: (2) the substance’s manufacture, used and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling.” Furosemide is not explicitly listed in section 205.603 as a synthetic substance, allowed for use in organic livestock production nor is it listed in section 205.604 as a prohibited substance.

**Regulatory: EPA/NIEHS/Other Sources**

**FDA:**
Code of Federal Regulations]
[Title 21, Volume 6]
[Revised as of April 1, 2001]
From the U.S. Government Printing Office via GPO Access
[CITE: 21CFR520.1010b]

[Page 134-135]

**TITLE 21--FOOD AND DRUGS**

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

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

Sec. 520.1010b Furosemide powder.

(a) Specifications. Furosemide powder is packaged in packets containing 2 grams of furosemide plus other inert ingredients.

(b) Sponsor. See No. 012799 in Sec. 510.600(c) of this chapter.

(c) Conditions of use. It is administered to dairy cattle alone, as a “top dressing” upon a small amount of feed or as a drench.

(1) Amount. 1 to 2 milligrams per pound of body weight but not to exceed one packet per animal, per day.

(2) Indications for use. The drug is used for the treatment of physiological parturient edema of the mammary gland and associated structures.

(3) Limitations. Treatment not to exceed 48 hours post-parturition. For oral use only. The individual dose is one packet administered once

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daily; when treatment is initiated with an injectable, at least a 12-
hour interval must follow before oral administration. Milk taken during
treatment and for 48 hours (four milkings) after the last treatment must
not be used for food. Cattle must not be slaughtered for food within 48
hours following last treatment. The drug, if given in excessive amounts
or over extended periods of time, may result in dehydration and
electrolyte imbalance. Federal law restricts this drug to use by or on
the order of a licensed veterinarian.

[43 FR 14647, Apr. 7, 1978, as amended at 47 FR 15327, Apr. 9, 1982]

[Code of Federal Regulations]
[Title 21, Volume 6]
[Revised as of April 1, 2001]
From the U.S. Government Printing Office via GPO Access
[CITE: 21CFR520.1010c]
Furosemide injection.

(a) Specifications. Each milliliter of sterile solution contains 50 milligrams of furosemide as the diethanolamine salt.

(b) Sponsor. See No. 012799 in Sec. 510.600(c) of this chapter for use in dogs and cats as in paragraph (c)(1) of this section, horses as in paragraph (c)(2)(i) of this section, and cattle as in paragraph (c)(3) of this section. See Nos. 000010 and 000864 in Sec. 510.600(c) for use in horses as in paragraph (c)(2)(ii) of this section. See No. 000010 in Sec. 510.600(c) of this chapter for use in dogs as in paragraph (c)(1) of this section.

(c) Conditions of use—(1) Dogs and cats. (i) It is used for the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.

(ii) The drug is administered intramuscularly or intravenously at a dosage of 12.5 to 25 milligrams per 10 pounds of body weight; once or twice daily after a 6- to 8-hour interval. The lower dosage is suggested for cats. The dosage should be adjusted to the individual animal's response. In refractory or severe edematous cases, the dosage may be doubled or increased by increments of 1 milligram per pound of body weight to establish the effective dose. The established effective dose should be administered once or twice daily on an intermittent daily schedule. Diuretic therapy should be discontinued after reduction of edema, or when necessary, maintained after determining a programmed dosage schedule to prevent recurrence.

(2) Horses. (i) It is used for the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.

(a) Administer intramuscularly or intravenously at 250 to 500 milligrams per animal once or twice daily at 6- to 8-hours intervals until desired results are achieved.

(b) Do not use in horses intended for food.

(ii) It is used for treatment of acute noninflammatory tissue edema.

(a) Administer intramuscularly or intravenously at 0.5 milligram per pound of body weight (1.0 milligram per kilogram); once or twice daily at 6- to 8-hour intervals.

(b) The dosage should be adjusted to the individual's response. In refractory or severe edematous cases, the dosage may be doubled or increased by increments of 1 milligram per pound of body weight to establish the effective dose. The established effective dose should be administered once or twice daily on an intermittent daily schedule, i.e., every other day or 2 to 4 consecutive days weekly. Concurrent therapy for treatment of systemic conditions causing edema (pulmonary congestion, ascites, cardiac insufficiency) should be instituted.

(3) Cattle. (i) It is used for the treatment of physiological parturient edema of the mammary gland and associated structures.

(ii) The drug is administered intramuscularly or intravenously at a dosage of 500 milligrams per animal once daily or 250 milligrams per animal twice daily at 12-hour intervals, treatment not to exceed 48 hours postpartum.
(iii) Milk taken during treatment and for 48 hours (four milkings) after the last treatment must not be used for food.
(iv) Cattle must not be slaughtered for food within 48 hours following last treatment.
(4) The drug if given in excessive amounts may result in dehydration and electrolyte imbalance.
(5) Federal law restricts this drug to use by or on the order of a licensed veterinarian.


HAZARD IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE - Inhalation, Eye/Skin Absorption and Ingestion.

CHEMICAL LISTING AS CARCINOGEN:

COMPONENT CAS No. Furosemide 54-31-9
NTP: not regulated
IARC: not regulated
OSHA: not regulated

EPA:
Status:
EPA Genetox Program 1988,
Negative: S cerevisiae gene conversion EPA Genetox Program 1988
Inconclusive: Histidine reversion-Ames test
Meets criteria for proposed OSHA Medical Records Rule

NFPA Hazard Rating:
Health (H): None
Flammability (F): None
Reactivity (R): None

Status Among U.S. Certifiers
Oregon does not have specific limitations on materials used for crops and livestock. If the materials comply with USDA regulations, they are deemed acceptable for use in the state of Oregon. (Contact- Ron McKay)

Pennsylvania is in accordance with guidelines proposed by OMRI. (Contact- Martha Melton- state certifier)

Minnesota does not have specific limitations on materials used for crops and livestock. If the materials comply with USDA regulations, they are deemed acceptable for use in the state of Minnesota. (Contact- Mary Hanks- state certifier)

International
IFOAM: not specifically mentioned in approved list
JAPAN: not specifically mentioned in approved list
EUROPEAN UNION: not specifically mentioned in approved list

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23 Directly referenced from http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html
25 Information was referenced from a phone interview with Ron McKay, State Certifier, June 5, 2002.
26 Information was referenced from a phone interview with Martha Melton, State Certifier, June 5, 2002
27 Information was referenced from a phone interview with Mary Hanks, State Certifier, June 12, 2002
28 Directly referenced from http://wwwifoam.org/standard/ibs_fin02.html
Manufacturers; Importers

Australia: Hoechst; Protea

Canada: Hoechst; Horner; Novopharm

Eire: Hoechst; Napp

France: Hoechst; Rorer

Germany: Azupharma; Brenner-Efeka; Bristol; Durachemie; Hexal; Hoechst; Klinge-Nattermann; Medice; Rorer; Sanorania; Siegfried; Winthrop

Netherlands: Hoechst; ICN

Italy: Hoechst; Lepetit; Scharper

South Africa: Arcana; Hoechst; Lennon; Rolab; Schwulst

Spain: Alter; Lasa; Hoechst

Sweden: A.L.; Benzon; Dumex; Hoechst

Switzerland: Hoechst; Mepha; Mundipharma; Schonenberger;

United Kingdom: Askbourne; Asta Medica; Berk; CP Pharmaceuticals; Cox; DDSA Pharmaceuticals; Evans; Fisons; Hoechst; Kerfoot; Norton; Rorer; Unimed

United States of America: Hoechst

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.

Furosemide may have interactions with Siberian Ginseng, Dandelion, Ephedra, Forskolin, Garlic, Ginseng, and Glucosamine. Most of these drugs used in conjunction with furosemide will lower the effects of furosemide.

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.

“It is extremely difficult to overdose with this medication. Toxic doses reported are over 100 times a typical oral dose of medication. It is important to realize that in the treatment of heart failure (this drug’s primary use), a crisis can arise at any time. Often giving an extra dose of oral medication can be a life saving procedure.”

31 Information referenced from http://www.wholehealthmd.com/refshelf/drugs_interact/0,1748,272,00.html
32 Directly referenced from http://www.vin.com/PetCare/Articles/VetHospital/M00585.htm
Acute and Chronic poisoning

**Ingestion** Oral ingestion is the usual means of exposure outside of a health care facility.

**Inhalation** Not relevant.

**Skin exposure** There is no appreciable dermal absorption.

**Eye contact** There is no appreciable absorption or local irritation.

**Parenteral exposure** Frusemide is used intravenously in acute volume overload states but would not be available outside of a health care facility. 33

Furosemide is generally not harmful to the environment or its inhabitants. This drug is not inhaled and skin exposure is irrelevant limiting potential toxological effects on humans and animals.

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

“The principal signs and symptoms of overdose with LASIX are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hypochloremic alkalosis, and are extensions of its diuretic action.

The acute toxicity of LASIX has been determined in mice, rats and dogs. In all three, the oral LD₅₀ exceeded 1000 mg/kg body weight, while the intravenous LD₅₀ ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats.

The concentration of LASIX in biological fluids associated with toxicity or death is not known.

Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy).

Hemodialysis does not accelerate furosemide elimination.

**HOW SUPPLIED**

LASIX (furosemide) Tablets 20 mg are supplied as white, oval, monogrammed tablets in Bottles of 100 (NDC 0039-0067-10), 500 (NDC 0039-0067-50), 1000 (NDC 0039-0067-70), and in Unit Dose Packs of 100 (NDC 0039-0067-11). The 20 mg tablets are imprinted with “Lasix®” on one side and “HOECHST” on the other.

LASIX Tablets 40 mg are supplied as white, round, monogrammed, scored tablets in Bottles of 100 (NDC 0039-0060-13), 500 (NDC 0039-0060-50), 1000 (NDC 0039-0060-70), and Unit Dose Packs of 100 (NDC 0039-0060-11). The 40 mg tablets are imprinted with “Lasix® 40” on one side and the Hoechst logo on the other.

LASIX Tablets 80 mg are supplied as white, round, monogrammed, facetted edge tablets in Bottles of 50 (NDC 0039-0066-05) and 500 (NDC 0039-0066-50). The 80 mg tablets are imprinted with “Lasix® 80” on one side and the Hoechst logo on the other.

33 Directly referenced from http://www.inchem.org/documents/pims/pharm/pim240.htm#SubSectionTitle:1.4.2%20%20Other%20numbers
Note: Dispense in well-closed, light-resistant containers. Exposure to light might cause a slight discoloration. Discolored tablets should not be dispensed.”

FIRE FIGHTING MEASURES
GENERAL HAZARD: 100% of the raw material is considered a poison by intravenous route; moderately toxic by ingestion and intraperitoneal routes.
FIRE FIGHTING INSTRUCTION: Water spray, dry chemical, carbon dioxide or foam as appropriate.
FIRE FIGHTING EQUIPMENT: Wear self-contained breathing apparatus and protective clothing.
HAZARDOUS COMBUSTION PRODUCTS: Very toxic fumes of Cl-, NOx and SOx.
Closed Cup Flash Pt.: NE
Open Cup Flash Pt.: NE
Fire Point: NE
Autoignition: NE
Lower Explosion Limit: NE
Upper Explosion Limit: NE
Fire and Explosion Data: NE

ACCIDENTAL RELEASE MEASURES
HANDLING AND STORAGE
CLEAN-UP: Wear recommended personal protective equipment. Use absorbent towels or booms to clean-up spill. Wipe surfaces clean and wash with soap and water.
When handling pharmaceutical products, avoid all contact and inhalation of dust, fumes, mist, and/or vapors associated with the product.
Store product below 40 øC (104 øF), preferably between 15 and 30 øC (59 - 86 øF).
Protect from freezing.
Protect from light.

EXPOSURE CONTROLS/PERSONAL PROTECTION
ENGINEERING CONTROLS:
Under indicated use, general room ventilation is usually satisfactory. Use local exhaust ventilation when necessary.

PERSONAL PROTECTION:
Respirators - With satisfactory ventilation, respiratory protection not usually required.
Eyes - Safety glasses or goggles recommended.
Gloves - Disposable latex gloves recommended.
Clothing - Disposable garments if direct skin contact is anticipated.

TRANSPORT INFORMATION
WASTE DISPOSAL - Waste product should be incinerated in accordance with federal, state and local regulations.
DOT Hazard Class: NE
Shipping Name: NE
Shipping Label: NE
UN/NA Number: NE

“Should a spill occur while you are handling this chemical, FIRST REMOVE ALL SOURCES OF IGNITION, then you should dampen the solid spill material with 60-70% ethanol and transfer the dampened material to a suitable container. Use absorbent paper dampened with 60-70% ethanol to pick up any remaining material. Seal the absorbent paper, and any of your clothes, which may be contaminated, in a vapor-tight plastic bag for eventual disposal. Solvent wash all contaminated surfaces with 60-70% ethanol followed by washing with a soap and water solution. Do not reenter the contaminated area until the Safety Officer (or other responsible person) has verified that the area has been properly cleaned.”

34 Directly referenced from http://www.aventispharma-us.com/PIs/Lasix_TXT.html
36 Directly referenced from http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

Human Toxicity Excerpts:

ABNORMALITIES FLUID & ELECTROLYTE IMBALANCE IS MOST COMMON FORM OF CLINICAL TOXICITY, SIDE EFFECTS UNRELATED TO PRIMARY DRUG ACTION ... ARE QUITE RARE. HYPERURICEMIA IS RELATIVELY COMMON.


OTHER REACTIONS INCL GI DISTURBANCES ... DEPRESSION OF FORMED ELEMENTS IN BLOOD, SKIN RASHES, PARESTHESIAS, & HEPATIC DYSFUNCTION. ... FUROSEMIDE ... IMPLICATED AS CAUSE OF ALLERGIC INTERSTITIAL NEPHRITIS, LEADING TO REVERSIBLE RENAL FAILURE.


DEC R IN CARBOHYDRATE TOLERANCE MAY OCCUR. ... TRANSIENT DEAFNESS HAS BEEN REPORTED WITH FUROSEMIDE.


... BLURRING OF VISION, POSTURAL HYPTENSION, NAUSEA, VOMITING, OR DIARRHEA MAY OCCUR. ... WEAKNESS, FATIGUE, LIGHT HEADEDNESS OR DIZZINESS, MUSCLE CRAMPS, THIRST, & URINARY FREQUENCY.


ADVERSE EFFECTS WHICH MAY RESULT FROM THERAPY WITH FUROSEMIDE INCL REDN OF RENAL, CEREBRAL, & CARDIAC BLOOD FLOW ... ELEVATION OF BLOOD URIC ACID & BLOOD SUGAR LEVELS, ALLERGIC REACTIONS, RARE CASES OF EXFOLIATIVE DERMATITIS, PRURITUS, & BLOOD DYSCRASIAS (THROMBOCYTOPENIA & LEUKOPENIA).


FUROSEMIDE, DIURETIC, HAS BEEN GIVEN SYSTEMICALLY & TESTED FOR EFFECT ON INTRAOCULAR PRESSURE IN ... NORMAL & GLAUCOMATOUS PATIENT IT HAS PRODUCED NO ELEVATION, BUT SMALL DECR IN PRESSURE IN GLAUCOMA.


OF 585 MEDICAL INPATIENTS TREATED WITH FUROSEMIDE, 123 HAD TOTAL OF 177 ADVERSE REACTIONS. MOST COMMON WERE HYPOVOLEMA (85 CASES), HYPERURICEMIA (54), & HYPOKALEMIA (21). MOST REACTIONS WERE MILD, & ONLY 3 PATIENTS HAD POTENTIALLY LIFE THREATENING EFFECTS.

[LOWE J ET AL; BR MED J 2 (AUG): 360-2 (1979)]**PEER REVIEWED**

TWENTY NINE CASES OF DEAFNESS ASSOC WITH ADMIN OF FUROSEMIDE REPORTED TO FDA ARE STUDIED. HAD BEEN ADMIN ORALLY OR IV IN DOSES OF 40 MG TO 21.6 G. DEAFNESS MAY BE TRANSIENT OR PERMANENT. MANY PT HAD RECEIVED OTHER OTOTOXIC DRUGS.

[GALLAGHER KL, JONES JK; ANN INTERN MED 91 (NOV): 744-5 (1979)]**PEER REVIEWED**
Furosemide is not known to be hepatotoxic in humans at normal therapeutic doses, but in vitro studies have shown that human liver microsomes are capable of converting furosemide to metabolites that bind irreversibly to microsomal proteins.

[DHHS/NTP; Toxicology and Carcinogenesis Studies of Furosemide in F344/N Rats and B6C3F1 Mice (Feed Studies) p.17 (1989) Technical Rpt Series No. 356 NIH Pub No. 89-2811]**PEER REVIEWED**

Too vigorous diuresis, as evidenced by rapid and excessive weight loss, may induce orthostatic hypotension or acute hypotensive episodes, and the patient's blood pressure should be closely monitored. Excessive dehydration is most likely to occur in geriatric patients and/or patients with chronic cardiac disease treated with prolonged sodium restriction or those receiving sympatholytic agents. The resultant hypovolemia may cause hemoconcentration, which could lead to circulatory collapse or thromboembolic episodes such as possibly fatal vascular thromboses and/or emboli. Pronounced reductions in plasma volume associated with rapid or excessive diuresis may also result in an abrupt fall in glomerular filtration rate and renal blood flow, which may be restored by replacement of fluid loss. Rarely, sudden death from cardiac arrest has been reported following iv or im administration of furosemide.


Potassium depletion occurs frequently in patients with secondary hyperaldosteronism which may be associated with cirrhosis or nephrosis and is particularly important in cirrhotic, nephrotic, or digitalized patients. Hypokalemia and hypochloremia may result in metabolic alkalosis, especially in patients with other losses of potassium and chloride due to vomiting, diarrhea, GI drainage, excessive sweating, paracentesis, or potassium losing renal diseases. In patients with cor pulmonale, alkalosis may cause compensatory respiratory depression.


Furosemide may cause a transient rise in BUN which is usually readily reversible upon withdrawal of the drug. Elevated BUN is especially likely to occur in patients with chronic renal disease. Hyperuricemia may result from furosemide administration and rarely gout has been precipitated; patients with a history of gout or elevated serum uric acid concentrations should be observed closely during therapy. However, large iv doses of furosemide may cause temporary uricosuria. Elevations of BUN and uric acid concentrations may be associated with dehydration, which should be avoided, particularly in patients with renal insufficiency. Allergic interstitial nephritis leading to reversible renal failure has been attributed to furosemide. Blood ammonia concentrations may be increased, especially in patients with preexisting elevations of blood ammonia.


Chronic administration of furosemide 50 mg/kg in rats has caused renal tubular degeneration. Calcification and scarring of the renal parenchyma has occurred in dogs receiving 10 mg/kg for 6 mo.


Tinnitus, reversible or permanent hearing impairment, or reversible deafness have occurred, usually following rapid iv or im administration of furosemide in doses greatly exceeding the usual therapeutic dose of 20 to 40 mg. Otic effects are most likely to occur in patients with severe impairment of renal function and/or in patients receiving other ototoxic drugs (eg, aminoglycosides). It has been postulated that administering furosemide by slow iv infusion rather than as a bolus may reduce the ototoxic effects of the drug by preventing high peak plasma concentrations; if high dose parenteral furosemide therapy is necessary in patients with severely impaired renal function, the manufacturers recommend that the drug be
infused in adults at a rate not exceeding 4 mg/min.

Adverse GI effects of furosemide include nausea, anorexia, oral and gastric irritation, vomiting, cramping, diarrhea, and constipation. Because furosemide oral solutions contain sorbitol, they may cause diarrhea, especially in children, when high dosages are administered. In children, mild to moderate abdominal pain has been reported after furosemide was administered iv. In addition, rare occurrences of sweet taste have been reported, but a causal relationship to the drug has not been established.

Furosemide may produce hyperglycemia and glycosuria, possibly as a result of hypokalemia, in patients with predisposition to diabetes. Rarely, precipitation of diabetes mellitus has been reported.

Diuretics, including furosemide, can increase serum total cholesterol concentrations in some patients; increases in low density lipoprotein cholesterol and/or very low density lipoprotein cholesterol subfractions appear to be principally responsible for these increases. In addition, the ratio of serum total cholesterol to high density lipoprotein cholesterol has been increased in some patients in whom total serum cholesterol did not appear to be elevated. Increases in serum triglyceride concentrations also can occur.

Adverse nervous system effects of furosemide include dizziness, lightheadedness, vertigo, headache, xanthopsia, blurred vision, and paresthesias.

Anemia, hemolytic anemia, leukopenia, neutropenia, and thrombocytopenia have occurred in patients receiving furosemide. In addition, rare cases of agranulocytosis and aplastic anemia have been reported.

Adverse dermatologic and/or hypersensitivity reactions to furosemide include purpura, photosensitivity, rash, urticaria, pruritus, exfoliative dermatitis, erythema multiforme, and necrotizing angiitis (vasculitis, cutaneous vasculitis). Patients with known sulfonamide sensitivity may show allergic reactions to furosemide. Anaphylaxis, manifested as urticaria, angioedema, and hypotension, occurred within 5 min after iv administration of furosemide in at least one patient; subsequent intradermal skin testing showed sensitivity to furosemide and other sulfonamides.

Transient pain at the injection site has been reported after im administration of furosemide.
Thrombophlebitis has occurred with iv administration.
Other adverse effects of furosemide include increased perspiration, weakness, fever, restlessness, muscle spasm, urinary bladder spasm, and urinary frequency. A few cases of flank and loin pain have been reported in adults receiving oral furosemide, possibly resulting from calyceal dilation, increased bladder pressure, or spasms caused by formation of calcium containing crystals in the urine. Intraperitoneal cholestatic jaundice and pancreatitis have also occurred in patients receiving furosemide. Furosemide may possibly exacerbate or activate systemic lupus erythematosus.


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.

LONG-TERM CARCINOGENICITY

2-YEAR (Dosed-Feed) (C55936)

(NTIS # PB90-106162) (PEER REVIEW 04/88)

RATS: FISCHER 344; MICE: B6C3F1

CARCINOGENESIS RESULTS

MALE RATS = EQUIVOCAL EVIDENCE

FEMALE RATS = NO EVIDENCE

MALE MICE = NO EVIDENCE

FEMALE MICE = SOME EVIDENCE

DOSE: R: 0,350,700, M: 0,700,1400 PPM/50 PER GROUP

HANDLING PROCEDURES

*ACUTE/CHRONIC HAZARDS:

When heated to decomposition this compound emits very toxic fumes of carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides and hydrogen chloride gas.

<table>
<thead>
<tr>
<th>ATC group</th>
<th>Group</th>
<th>Environmental evaluation</th>
<th>Pharmaceuticals that may be problematic</th>
</tr>
</thead>
</table>

37 Directly referenced from http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAzba4Ob:1
38 Directly referenced from http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html
| A | Alimentary tract and metabolism | No environmental effects expected | - |
| B | Blood and bloodforming organs | No environmental effects expected | - |
| C | Cardiovascular system | Possible environmental effects | Furosemide Bendroflumethiazide |
| D | Dermatologicals | Cannot be assessed | (Ketoconazole) |
| G | Genito urinary system and sex hormones | Possible environmental effects | Estrogens |
| H | Systemic hormonal preparations, excl. sex hormones | Cannot be assessed | (Corticosteroids) |
| J | General antiinfectives for systemic use | Possible environmental effects | Various antibiotics |
| L | Antineoplastic and immunomodulating agents | Possible environmental effects | - |
| M | Musculo-skeletal system | Possible environmental effects | Ibuprofen |
| N | Nervous system | Possible environmental effects | Paracetamol Several compounds cannot be assessed |
| P | Antiparacitic products, insecticides and repellants | No environmental effects expected | - |
| R | Respiratory system | Cannot be assessed | - |
| S | Sensory organs | No environmental effects expected | - |
| V | Various | No environmental effects expected | - |

“Two candidates for potential environmental problems from the ATC group for Cardiovascular system (furosemide and bendroflumethiazide) are both used in large amounts, but there was insufficient data to assess the compounds.”
Attention is drawn to the fact that none of the data sets of measured concentrations are from Denmark and both local and regional differences may affect the emission pattern.

In the project no data on sorption properties or toxicity of pharmaceuticals in soil have been identified, which could be used for assessment of toxicity in soil environment. Several of the pharmaceuticals on L25 have a potential for sorption to sludge, and the degradability in soil or sludge is not known or poorly investigated.

The consumption of pharmaceuticals in hospitals is not included in the statistic. Emissions from hospitals and other treatment centres may act as point sources presumably with higher concentrations of pharmaceuticals and metabolites compared to the average occurrence in wastewater.

Generally, the concentrations found in the environment and other sources of non-therapeutic exposure are considerably below the therapeutic doses, normally administered to humans. This does not, however, exclude the possibility that there may be relevant exposure scenarios leading to fx. long term or combination effects, or effects to vulnerable groups.”

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

Carbonic anhydrase (CA) inhibitors
Sulfonamide derivatives (See the table below).
Sulfonamide group (-SO2NH2) is essential for activity.

Acetazolamide
Dichlorphenamide
Methazolamide

Inhibitors of Carbonic Anhydrase
This class of diuretics inhibits carbonic anhydrase in the membrane and cytoplasm of the epithelial cells. The primary site of action is in proximal tubules. In the proximal tubule, Na+-H+ antiport in the apical membrane of epithelial cells transports H+ into tubular lumen in exchange for Na+ movement into the cytoplasm. Na+ in the cytoplasm is pumped out to the interstitium by sodium pump. H+ in the lumen reacts with HCO3- to form H2CO3. H2CO3 is dehydrated to CO2 and H2O. This reaction is catalyzed by carbonic anhydrase in the luminal membrane. Both CO2 and H2O can permeate into cells, and rehydrate to form H2CO3. The rehydration is catalyzed by the cytoplasmic carbonic anhydrase. H2CO3 dissociates to form H+ which is secreted into lumen, and HCO3- which is transported into interstitium. Inhibition of anhydrase thus inhibits HCO3- reabsorption. Accumulation of HCO3- in the tubular lumen subsequently inhibits Na+-H+ exchange and Na+ reabsorption. The increase in sodium concentration in the tubular fluid may be compensated partially by increased NaCl reabsorption in later segments of the tubule. Thus, the diuretic effect of the carbonic anhydrase inhibitors is mild.

Clinical indications
(i) Glaucoma
(ii) Treatment of cystinuria, and enhance excretion of uric acid and other organic acids.
(iii) Metabolic alkalosis

ATP
CA CA
HCO3-
H+
H2O + CO2 H2O + CO2
H+ + HCO3-
Na+
Na+
K+

CA Inhibitors
Proximal convoluted tubule
Lumen Interstitium
epithelial cell
Na+
(iv) Acute mountain sickness

Major side effects and toxicity
(i) Electrolyte imbalance: Hyperchloremic metabolic acidosis is the most common side effect.
(ii) Renal stones
(iii) Central nerve system effects: drowsiness and paresthesias.
(iv) Allergic reactions to sulfonamides such as rash, fever, and interstitial nephritis.

Osmotic diuretics
Glycerin
Isosorbide
Mannitol
Urea

Osmotic Diuretics
R, renal excretion; M metabolism; ID, insufficient data.
Osmotic diuretics are substances to which the tubule epithelial cell membrane has limited permeability. When administered (often in a large dosage), osmotic diuretics significantly increase the osmolarity of plasma and tubular fluid. The osmotic force thus generated prevents water reabsorption, and also extracts water from the intracellular compartment, expands extracellular fluid volume and increases renal blood flow resulting in reduced medulla toxicity. The primary sites of action for osmotic diuretics are the Loop of Henle and the proximal tubule where the membrane is most permeable to water.

Clinical indications
(i) To increase urine volume in some patients with acute renal failure caused by ischemia, nephrotoxins, hemoglobinuria and myoglobinuria (test for responsiveness).
(ii) Reduction of intracranial pressure before and after neurosurgery and in neurological conditions.
(iii) Reduction of intraocular pressure before ophthalmologic procedures and during acute attack of glaucoma.

Major side effect and toxicity
(i) Water and electrolyte imbalance: excessive loss of more water relative to sodium may cause dehydration and hypernatremia.
(ii) Expansion of extracellular fluid volume may result in hyponatremia causing central nerve system symptoms such as nausea, headache, and vomiting. In patients with congestive heart failure, expansion of extracellular volume may produce pulmonary edema.

Thiazides
Thiazides are also called benzothiadiazides. Thiazides are sulfonamide derivatives. Thiazides inhibit a Na+-Cl- symport in the luminal membrane of the epithelial cells in the distal convoluted tubule. Thus, Thiazides inhibit NaCl reabsorption in the distal convoluted tubule, and may have a small effect on the NaCl reabsorption in the proximal tubule. Thiazides enhance Ca++ reabsorption in the distal convoluted tubule by inhibiting Na+ entry and thus enhancing the activity of Na+-Ca++ exchanger in the basolateral membrane of epithelial cells.

Major clinical indications
(i) Hypertension.
(ii) Edema associated with congestive heart failure, hepatic cirrhosis and renal diseases.
(iii) Nephrolithiasis due to hypercalciuria
(iv) Nephrogenic diabetes insipidus.

Major side effects and toxicity
(i) Water and electrolyte imbalance is the major side effect. Hypokalemic metabolic alkalosis, and hyperuricemia. Also may cause extracellular volume depletion, hyponatremia, hypochloremia, and hypomagnesemia. These effects are similar to that caused by loop diuretics.
Hypercalcemia.

Hyponatremia is more common with thiazides than with loop diuretics.

(ii) Thiazides may impair glucose tolerance and hyperglycemia. Hyperglycemia can be reduced when K+ is administered together with thiazides, suggesting that hyperglycemia may be related to hypokelemia.

(iii) Thiazides may cause hyperlipidemia. Plasma LDL, cholesterol and triglycerides are increased.

(iv) Allergic reactions to sulfonamides

(v) CNS symptoms and impotence can be seen but not common.

Spironolactone is the only available aldosterone antagonist in US. An metabolite of spironolactone, canrenone, is also active and has a half-life of about 16 hours. Aldosterone, by binding to its receptor in the cytoplasm of epithelial cells in collecting tubule and duct, increases expression and function of Na+ channel and sodium pump, and thus enhances sodium reabsorption (see "Na+ channel inhibitors" above). Spironolactone competitively inhibits the binding of aldosterone to its receptor and abolishes its biological effects.

**Major clinical indications**

(i) Used in combination with loop diuretics and thiazides in treatment of edema and hypertension. Spironolactone enhances Na+ excretion and reduces K+ wasting.

(ii) Treatment of primary hyperaldosteronism (such as adrenal adenomas).

(iii) Treatment of edema associated with secondary hyperaldosteronism (such as cardiac failure, hepatic cirrhosis and nephrotic syndrome). Spironolactone is the diuretic of choice in patients with hepatic cirrhosis.

**Major side effects and toxicity**

(i) Hyperkalemia

(ii) Metabolic acidosis in cirrhotic patients

(iii) Due to its steroid structure, Spironolactone may cause gynecomastia, impotence, and hirsutism.

(iv) CNS symptoms.  

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

Furosemide’s sensitivity to light and the detrimental decomposition byproducts make this compound fairly incompatible with a system to sustainable agriculture. Furosemide is generally safe unless burned. When heated to decomposition this compound emits very toxic fumes of carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides and hydrogen chloride gas.  

“Carbon monoxide is a colorless, odorless, tasteless and toxic gas produced as a by-product of combustion.” Extensive research has not been conducted on whether or not furosemide is detrimental to the environment. Furosemide may cause potential environmental problems primarily due to its decomposition byproducts. Information is limited on exact environmental contamination problems or concerns of furosemide.

**TAP Reviewer Discussion**

**Reviewer 1 [Ph.D. Professor Protein-based antimicrobials, biogenic amines in food and beverages, and applied studies with beer and wine, Northwest US]**

**Reviewer 1 Comments on the Database**

The application fails to provide a description of how the drug is actually manufactured, which would include the chemicals and processes employed. This information would be useful to determine if the manufacturing process is in harmony with organic handling practices.

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41 Directly referenced from http://www.uic.edu/classes/pcol/pcol425/restricted/Du/diuretics.PDF


43 Directly referenced from http://freenet.msp.mn.us/people/guestb/pubed/cofaq.html
More specific information is needed on the residence time (half-life) of the drug in the animal after administration. There is mention in the application that 48 hours are required after drug administration before either milk is taken or the animal is slaughtered. The concern lies that there is a significant amount still in the animal when it is slaughtered. The application mentions that the thermal decomposition products of furosemide are "very toxic fumes." The question that this raises is if an animal is slaughtered for meat production that has residual furosemide, could cooking that meat release toxic fumes?

**Reviewer 1 Conclusion**

Furosemide as a synthetic substance may be allowed for organic livestock production if criteria from the National List are met. Furosemide is clearly a chemically derived drug and does not have a natural source or origin. However, there are few if any effective naturally occurring diuretics. Dandelion and asparagus are known to contain components that have diuretic effects, however their effectiveness in managing severe edema is not known. The diuretic effects of caffeine are well known, however its use in a veterinary application for edema has not to my knowledge been described.

There is no evidence that furosemide has any preservative effect or could be used to enhance the sensory characteristics of either milk or meat. The drug cannot be classified as GRAS. It cannot be unequivocally stated that furosemide is essential for organic production. The drug is useful for managing severe edema in cattle, which is not a routine production practice but rather an emergency situation.

**Reviewer 1 Recommendation Advised to the NOSB**

In conclusion, the application does not convincingly convey that furosemide meets the criteria for inclusion into the National List.

**Reviewer 2 Comments on the Database**

None mentioned in review.

**Reviewer 2 Conclusion**

The overall need for furosemide in the organic arena is questionable. There are not necessarily any particular concerns regarding furosemide other than what has been stated in the report itself, but there are many alternatives that are very effective diuretics, thus negating the overall need for furosemide:

1) Homeopathy: Apis mel
2) Herbals: Juniper Berries, Parsley, Cayenne.

Others to consider: Agrimony, Astragalus, Atractylodes, Birch, Broad Bean, Butcher's Broom, Corn Silk, Dandelion, Fumitory, Parthenium, Pygeum, Seneca, Uva Ursi, Violet.
3) Topical natural essential oil liniments.

Regarding whether or not furosemide is synthetic or non-synthetic, it is difficult to conclude. Furosemide is assumed to be synthetic.

**Reviewer 2 Recommendation Advised to the NOSB**

Furosemide can be added to the NOSB list of allowed substances with restrictions. Restrictions should include label directions and usage as a last resort if all other natural alternatives do not work or cannot be obtained. There are a number very effective natural alternatives that could be listed for the veterinarians to pick from so they start to learn how to use better and more natural therapies. Lower profit margins for the veterinarian should not be an issue when the discussion concerns organic livestock.
Reviewer 3  [Ph.D. Meat Science, M.S. Ruminant Nutrition, research, teaching and extension activities related to the quality and safety of fresh and processed foods, particularly, muscle food products. Rocky Mountain Region US]

Comments on Database

In general, the TAP Review document is complete and well presented. It includes pertinent information regarding furosemide use in livestock species of interest, as well as humans and studies with laboratory animals.

Under the section titled “Status, Historic Use by Organic Farmers” the TAP Review lists the use of Lasix at the 1980-81 Houston Livestock Show to “allow” animals to make the show weight. This section is largely irrelevant to the “Historic Use by Organic Farmers” and should be deleted.

Under the section titled “Status, Historic Use by Organic Farmers” the TAP Review lists the use of furosemide to prevent exercise-induced pulmonary hemorrhage in race horses. This section is largely irrelevant to the “Historic Use by Organic Farmers” and should also be deleted.

OFPA Criteria Evaluation

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems.
   The TAP Review indicates that furosemide may have interactions with Siberian Ginseng, Dandelion, Ephedra, Forskolin, Garlic, Ginseng, and Glucosamine, and, that most of these drugs, used in conjunction with furosemide, will lower the effects of furosemide. However, given that furosemide would most likely be used to treat 1) constrictive udder edema in immediately post-partum lactating dairy cows and 2) pulmonary edema associated with congestive heart failure in food animals, it is unlikely that the aforementioned interactions would be of significance in organic agricultural production systems.

(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.
   I agree with the criteria evaluation.

(3) The probability of environmental contamination during manufacture, use, misuse or disposal of such substance.
   I agree with the criteria evaluation.

   This segment of the TAP review is especially well documented in regards to therapeutic doses of furosemides given to humans. The risk to humans due to accidental exposure is minimal.

(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.
   Furosemides produce an acute and measurable biological effect, thus their preferred use as a therapeutic diuretic. Furosemides are relatively harmless to humans and other animals via accidental exposure. However, there is some concern that the breakdown products of furosemide are environmentally harmful and not well studied. They should be used under supervision of a licensed veterinarian, in which case their misuse and subsequent chances of detrimental effects on the agroecosystem are minimal. It should be noted, however, that they are readily available via the Internet.

(6) The alternatives to using the substance in terms of practices or other available materials.
Most alternative diuretic compounds are also synthetic. Furosemides are preferred due to their effectiveness and large safety factor. Although, alternative natural diuretic treatments are available, they are less effective.

(7) Its compatibility with a system of sustainable agriculture.
Furosemides are effective for treatment of acute edema in livestock – primarily 1) constrictive udder edema in immediately post-partum lactating dairy cows and 2) pulmonary edema associated with congestive heart failure in food animals. They are apparently cleared from tissues, including milk, within 48 hours. In my opinion, infrequent and non-regular used of furosemides may be consistent with sustainable agricultural systems. My primary concern, however, is that more frequent and regular use of furosemides would indicate a breakdown in the sustainability of the agricultural system, and a reliance on a synthetic compound for sustained production. This would not be consistent with the spirit of the Federal Organic Foods Production Act of 1990.

Reviewer 3 Conclusion
Furosemides are effective for the treatment of acute edema in food animal livestock species. Acute edema, however, should be a rare occurrence in sustainable agricultural systems, regardless of the organic certification status of the farm. Use of furosemides, therefore, should not be allowed in the production of organic livestock products, including meat and dairy products.

Reviewer 3 Recommendation Advised to the NOSB:
The substance is Synthetic. For Livestock, the substance should be Not Added to the National List.

TAP Conclusion
All three TAP reviewers found furosemide to be a synthetic material. Two reviewers support allowance of the substance in livestock with restrictions, while the other believes it should NOT be included on the list and should not be allowed with or without restrictions. Specific concerns included the belief that furosemide does not meet the criteria for inclusion into the National List, there is not sufficient need for furosemide use in organic production and there are a number of available alternatives that are more compatible with organic standards.
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