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

Document Type:

☒ **National List Petition or Petition Update**

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

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

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

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

☐ **Technical Report**

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

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

Contractor names and dates completed are available in the report.

National List Manager
USDA/AMS/NOP, Standards Division
1400 Independence Ave. SW
Room 2648-So., Ag Stop 0268
Washington, DC 20250-0268
Sent via e-mail/link

February 6, 2024

Re: Petition to Add Meloxicam to the National List, §205.603 - Synthetic substances allowed for use in organic livestock production

Dear National List Manager,

This petition is the product of unprecedented pre-market collaboration of multiple organizations who have independently and collectively concluded that the interests of optimizing humane animal care for organically managed livestock required significant action to effect positive change. Such collaboration has been done in the interest of providing the best and most humane care possible for our organically managed livestock.

The objective of this petition is to provide an essential and effective means of conscientious pain management for livestock managed by organic producers. Collectively, we have gathered information and use case needs from producers, veterinarians (both within and without our respective companies), manufacturers, and other stakeholders in advance of developing this petition to ensure that the degree of need was indeed substantive. We intend on providing substantive public comment in support of this petition through both written and oral means as opportunities arise.

It is the utmost concern and responsibility for organic livestock operators to minimize the incidence of pain for the livestock in their charge and to actively participate in the pain management of those animals through responsible practice of animal welfare, veterinary procedure, and injury, accident, or disease prevention.

While all drug approval is under the authority of the Food and Drug Administration (FDA), it is the United States Department of Agriculture (USDA) through the National Organic Program (NOP) that allows for the use of those legally authorized drugs within certified organic livestock production. The very nature of the NOP and the certified organic industry mandates that not all substances or drugs in conventional use are necessary within the rubric of organic agriculture and handling in general and organic livestock in particular. Having said that, any pain mitigation management tools, especially drugs, need to be considered by the organic industry, the NOP, and the NOSB to assure that certified organic livestock are not neglected in receiving optimal care or left to unnecessarily suffer from pain.

The petitioners, who are not the drug manufacturer but long standing certified organic operators throughout the U.S., believe there is overwhelming justification for adding **Meloxicam** on the National List at **§205.603** as a synthetic substance allowed for use in organic livestock production, under the OFPA category ***Livestock parasiticides and medicines*****.**

Meloxicam is not entirely different from other approved and allowed pain management substances available for use by certified organic livestock producers; however, Meloxicam is more effective,

especially when compared to the efficacy of nonsynthetic tinctures and remedies. Meloxicam, in most cases, is easier to administer and less invasive to the animal than existing organic options and has longer lasting effects.

All indications are that the environmental impacts of Meloxicam's manufacturing and use are minimal, and the substance is also commonly prescribed for human use, also minimizing concerns for human health as well.

We, the petitioners, request that this petition be considered forthwith, in the hope that your consideration and approval can be completed expeditiously such that the benefits of Meloxicam can be brought to the thousands of animals in our sector's collecting stewardship in the shortest order possible. We care for our farms and animals deeply and sincerely believe Meloxicam not only meets the requirements for addition to the National List but that we also have a duty to bring its benefits for humane animal care to our animals as swiftly as possible.

We remain ready to respond to any and all requests for additional information in support of this petition from the NOP, National Organic Standards Board, or the Livestock or Materials Subcommittees as questions arise.

We sincerely thank you for your consideration.

***Meggan Hain**, CROPP Cooperative/Organic Valley/Organic Prairie*
***Megan Sutton**, Horizon Organic Dairy*
***Britt Lundgren**, Lactalis/Stonyfield Farms*
***Dr. Juan Velez**, Aurora Organic Dairy*

Petition to Add Meloxicam to the National List of Allowed Substances for Use in Organic Production

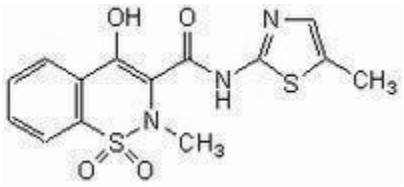
Item A:

This petition seeks inclusion of **Meloxicam** on the National List (NL) at **§205.603** as **a synthetic substance allowed for use in organic livestock production**. This material falls under the OFPA category ***Livestock parasiticides and medicines*.**

Item B:

1. Substance Name:

Common Name: Meloxicam
Generic Names: Mobic (sometimes Metacam, Movalis, Maxicam, Anjeso (I.v. form), or Vivlodex)
CAS Number: 71125-38-7
Empirical Formula: C14H13N3O4S2; 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3- carboxamide-1,1-dioxide



2. Petitioner and Manufacturer Information:

Petitioners:
Meggan Hain, CROPP Cooperative/Organic Valley/Organic Prairie
Megan Sutton, Horizon Organic Dairy
Britt Lundgren, Lactalis Yogurt US/Stonyfield Farms
Dr. Juan Velez, Aurora Organic Dairy

Petition Primary Contact:
Meggan Hain
Managing Veterinarian and Animal Care Specialist
608-625-3940
Meggan.Hain@organicvalley.coop

Note: This petition is organized, prepared, and submitted by a group of certified organic farmers, organic handlers, and other organic industry stakeholders and interested parties. It is not a petition from manufacturers of this substance. No marketers or manufacturers have actively contributed to the preparation of this petition nor the content it contains. The petitioners have not had access to any Confidential Business or Manufacturing information from any manufacturers of this substance.

Identified Manufacturers Include:

Mobic:
Boehringer Ingelheim Pharma GmbH & Co. KG Ingelheim, Germany
Boehringer Ingelheim Promeco S.A. de C.V., Mexico City, Mexico
800-243-0127
https://www.boehringer-ingelheim.com/

Vivlodex:
Manufactured (under license from iCeutica Pty Ltd.) for and Distributed by: Iroko Pharmaceuticals, LLC Philadelphia, PA 19112 Copyright 2015 Iroko Pharmaceuticals, LLC
Iroko Pharmaceuticals, LLC One Kew Place 150 Rouse Boulevard Philadelphia, PA 19112
267-546-3003
http://iceutica.com/

Anjeso:
Baudax Bio, Inc. Malvern, PA 19355 USA Made in Italy
484-395-2440
https://www.baudaxbio.com/

Qmiiz ODT:
Manufactured for: TerSera Therapeutics LLC, Deerfield, IL 60015 Manufactured by: Catalent Pharma Solutions, Limited, Swindon, Wilshire, SN5 8RU, UK QMIIZ™ ODT is a trademark of TerSera Therapeutics LLC. © 2021 TerSera Therapeutics LLC
877-587-1835
https://biologics.catalent.com/

Veterinary/human tablets:
Carlsbad Technology: Yung Shin Pharmaceutics, Taiwan
760-431-8284
http://carlsbadtech.com/

Unichem Pharmaceuticals: Goa, India
Cipla USA, Inc.: Mumbai, India
866-931-0704
https://unichemusa.com/

Zydus Pharmaceuticals: Ahmedabad, India
877-993-8779
https://zydususa.com/

3. <u>Intended or Current Use</u>:

Meloxicam is a long-lasting nonsteroidal anti-inflammatory drug (NSAID) with preferential COX-2 inhibition used primarily to treat pain and inflammation.

The primary method of administration is orally in a pill form; injectable forms are used in some instances.

COX-2 inhibitors are a class of NSAIDs as effective as traditional NSAIDs with fewer gastrointestinal side effects. Of the class, Meloxicam exhibits a longer therapeutic effect to relieve pain allowing for fewer treatments in a specified period of time. Meloxicam can be effective as a pain mitigating drug with one treatment, thereby imposing less stress on the patient which occurs with each treatment intervention. Meloxicam also treats low grade fever.

Meloxicam was approved for medical use in the United States in 2000. Its main use is for the treatment of pain and inflammation associated with osteoarthritis and rheumatic diseases. Side effects can include abdominal pain, dizziness, swelling, headache, rash, heart disease, stroke, kidney problems and stomach ulcers. It is not recommended for use in the last trimester of pregnancy. The oral form is not recommended for cats.

The typical dosage rate in adult humans is from 5 to 15 mg orally once per day. The usual dosage rate in dogs is 0.05 to 0.1 mg per lb.

Common Usage in Conventional Livestock:
Meloxicam is used widely in conventional dairy for the treatment of pain associated with disbudding in calves. This medication is more ideal than alternatives for this purpose as it has a long therapeutic effect of 24-48 hrs with a single dose. It is easy to administer orally and does not require additional technical skills (unlike Flunixin injectable which requires an intravenous injection by label). Meloxicam does not have significant health concerns when handled by animal caretakers.

Disbudding, debudding, and dehorning are forms of a practice commonly called 'dehorning' depending on the age of the animal and development of the animal's horn structure. The first two are the preferred procedures as they are performed at earlier stages of life where only soft tissue is involved, and no true horn or bone is present. Horns are typically removed from dairy cattle as animal welfare and caregiver safety practices to decrease the incidence of injury and even death.

Alternatives currently allowed in organic production

Flunixin (injectable and pour-on): Flunixin injectable is only labeled for intravenous use in cattle. It can cause significant reaction in the tissues resulting in variable drug withdrawal times or worse including abscesses or clostridial infections. Flunixin pour-on is much easier to administer but must be handled with significant care to avoid absorption by the caretakers applying it.

Aspirin (oral): While aspirin is a pill which is easy to administer orally, it is quickly metabolized in cattle and provides a therapeutic effect of only up to six hours of pain relief with a single dose.

Pain relief from natural brand-name remedies, home remedies, or tinctures have shown short lived and inconsistent results in scientific studies. A study published in the Journal of Dairy Science in 2022 (Appendix 1) found "white willow bark … unsuitable for producing analgesia in calves". The

same research group published a study in the journal Translational Animal Science in 2021 (Appendix 2) where they evaluated various herbal therapies "to alleviate acute pain and stress of disbudded dairy calves under organic management" finding that orally administered herbal treatments did not eliminate "acute pain in disbudded calves" and that 'results also suggest that additional analgesic may be required to properly manage disbudding pain effectively."

Natural brand name and home herbal tinctures and remedies are not likely to be used by veterinarians and not an acceptable pain management control under most dairy animal welfare programs.

With growing public awareness that cattle experience pain, the body of scientific literature on disbudding pain in dairy calves is significant. Many of these studies have shown the effectiveness of Meloxicam used along with lidocaine to control immediate and long-term pain associated with disbudding and to prevent 'wind-up' which is an escalation of pain due to poor control. In addition, past public comment consistently demonstrates the public's concern for dairy animal management which makes it imperative to provide effective pain control for routine animal management procedures which cause pain such as disbudding.

Phillips and Heinz (Appendix 3), in a review on practices in Organic Dairy Production, report on a publication published in 2011 that questions the value of horn removal related to animal and human safety, but they note that there were no studies on horned dairy cattle in the US to evaluate that theory and that 'preserving horns as a strategy to enhance dairy cattle welfare is insufficiently investigated'.

The use of polled (naturally without horns) genetics represents a potential alternative to dehorning. However, selecting for this one genetic trait would be slow to implement over many generations due to the low prevalence of polled genetics in most dairy cattle genetic lines. Emphasizing this as a primary breeding selection practice could result in inbreeding and pose an increased risk of undesirable recessive traits in the population. Such an emphasis, while possible, would limit genetic improvement in production traits such as output, efficiency of production, and the genetic adaptability to grass-based systems of production.

4. <u>Intended Activities and Application Rate</u>:

This petition requests the listing of Meloxicam on the NL at **§205.603** as a synthetic substance allowed for use in organic livestock production. This material falls under the category ***Livestock parasiticides and medicines*.**

Meloxicam, if added to the NL, would be a potential tool of the veterinarian and management of organic livestock operations to treat pain and inflammation in organic livestock. Meloxicam would be effective in the treatment of acute pain related to some veterinary procedures such as disbudding, debudding, dehorning, castration, or surgery, or in the treatment of chronic pain from conditions such as lameness, arthritis, and other musculoskeletal injuries and diseases.

Meloxicam provides a longer therapeutic effect (half-life) in the animal's system to treat pain, often with single dose treatment in acute cases, thereby improving the welfare and well-being of the animal compared to the other pain management substances which are included on the National List and used in similar circumstances.

Offered in oral tablet form with a longer half-life in the tissues there is a longer time period between treatments, Meloxicam provides an easier and more effective administration of a pain management treatment for the welfare of the animal and less potential damage to the environment and farm ecosystem.

The usual dose for pain relief in cows and calves is 1 mg/kg (0.45 mg/lb).

The accepted withdrawal times for Meloxicam are 96 hours for milk and between 15 and 21 days for meat. In the typical doubling of established withdrawal times being allowed in organic production, the withdrawal times would be 192 hours (8 days) for milk and up to 42 days for meat. Proper and adequate on-farm use records would need to be maintained by the operator.

Treatment of Pain Management required for Animal Welfare:

The control of pain in certified organic animals is an important feature of animal welfare and should be aspired to in all cases needed especially within a system of sustainable agriculture that espouses high ethical values.

The primary use for Meloxicam in the certified organic sector would be to provide prolonged pain relief in animals undergoing procedures such as disbudding/dehorning. It would be used at the time of the primary procedure to provide up to 48 hours of pain relief prior to needing another dose. It could be used also for other pain management incidents such as castration, periparturient pain, or injuries, particularly skeletomuscular ailments.

Pain relief in certified organic animals is limited to natural remedies or veterinary prescription items, allowed on NL §205.603, such as lidocaine, flunixin, butorphanol and xylazine. These are administered primarily by injection and generally have a 2 to 6-hour range of time of therapeutic effect. Aspirin is also allowed; however, due to its pharmacologic nature, is poorly utilized in ruminants.

Natural products marketed for pain relief management, tinctures and other herbal and natural remedies have generally been shown to be short lived and inconsistent in research and veterinarians are untrained in natural remedies and less likely to prescribe them.

Increasingly, animal welfare oversight programs such as Farmers Assuring Responsible Management (FARM 4, Appendix 4) require documented pain management procedures, in some cases from multiple sources. One example requiring multiple sources of administered pain management is disbudding of calves prior to 8 weeks of age. In FARM 4 (Appendix 4), Meloxicam is the only substance listed specifically for systemic pain relief associated with this procedure. Natural remedies for treatment of pain management are not included in most dairy animal welfare programs.

While there are already a few synthetics allowed for analgesia and anesthesia to reduce pain, there are none that have any sustained release as does Meloxicam. Consumers are sensitive to the utmost wellbeing of certified organic livestock and expect that animals do not endure unnecessary pain or stress while being raised in the certified organic system.

Meloxicam is not arguably different from other approved pain management tools; however, Meloxicam is more effective, easier to administer with less treatments needed, less invasive on the animal with no injection needed (decreasing the risk of disease transmission), relatively inexpensive, and an easy tool to adopt.

Finally, Meloxicam is an accepted tool for pain management of livestock in conventional operations and it is being used extensively. While use of a substance, especially a drug, should not be allowed in certified organic production simply because it is used in comparable conventional operations, the organic industry should not let itself be put into a position of being behind conventional livestock operations in their ability to satisfy the animal welfare needs of the animals under their care, especially in the case of pain management.

Meloxicam could become the preferred treatment for many procedures, including but not limited to, various forms of dehorning, castration, and musculoskeletal injuries such as some types of lameness.

FDA does screen for this drug in slaughter residue testing and there have been animals with positive residue tests reported. The FDA National Residue Program (NRP) was reporting positive Meloxicam residue samples in domestic livestock (1 bull and 3 dairy cows) tested at slaughter in the US at least as early as 2016 (Appendix 5). In 2022, the FDA reported meloxicam residue in the kidney tissue of veal calf sold and slaughtered from a dairy farm in Pennsylvania (Appendix 6). Proper recording of the use of Meloxicam would need to be recorded on the farm for both organic withdrawal and commercial slaughter withdrawal of treated animals.

5. Manufacturing Process:

This petition is submitted by certified organic livestock producers and supporters who believe that Meloxicam to the NL is in the best interest of organic producers, the organic livestock of which they are stewards, and the organic industry as a whole. No manufacturers participated in or contributed to the preparation of this petition. As a result, the manufacturing information provided below is compiled from extensive internet searches, including but not limited to websites for the United States Food and Drug Administration (FDA), the United States National Institute of Health (NIH), the Chemistry Book, Merck Index, and various scientific journals, and interviews. We cannot state that this information is exactly the precursor and manufacturing process for any specific manufacturer of this generic drug.

Precursor substances
Benzothiazolo-3(2H)-one-1,1-dioxide and methyl chloroacetate.

Manufacturing process
Reaction of benzothiazolo-3(2H)-one-1,1-dioxide with methyl chloroacetate gives the methyl 2(3H)-acetate derivative, which is isomerized with sodium methoxide in toluene-tert-butanol yielding methyl 4-hydroxy-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide. Subsequent methylation with methyl iodide in methanol yields the 2-methyl compound. Finally, this compound is treated with 2-amino-5-methylthiazole in xylene.
From: Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V3 51 (2003)
(Appendix 7)

Methyl chloroacetate (CAS 96-34-4)
According to Chemical Book, Methyl chloroacetate is prepared by esterification of chloroacetic acid with methanol. "Methanol and chloroacetic acid are uniformly mixed in a weight ratio of 0.366:1, heated with stirring, and the esterification reaction is carried out at 105-110 °C. In the reaction

process, the ternary azeotrope of methyl chloroacetate, water and methanol is continuously steamed, layered through the ester separator, the separated methanol and water are returned to the reaction pot, and the separated crude ester is made of sodium carbonate. neutralize. The neutralized crude ester is firstly cut out the 130°C fraction by atmospheric distillation, and then subjected to vacuum distillation to collect the 65°C (8kPa) fraction, which is the finished product of methyl chloroacetate. The yield is about 96%." (Appendix 8)

Benzothiazolo-3(2H)-one-1,1-dioxide
The FDA and NIH documents we were able to review regarding Meloxicam listed Benzothiazolo-3(2H)-one-1,1-dioxide as a precursor but a link to this substance was not provided, as it was to the other precursor and the intermediary substances in the manufacturing process. (For example, Appendix 7). In further searching, we could not find a CAS number for this substance, and it was not found in either the Chemical Bank database or the Merck Index.

Environmental impact
Review of the National Library of Medicine, including the Hazardous Substances Data Bank (HSDB) revealed no concerns generated environmental impact concerns from the manufacturing process, nor have any of the references noted in this petition suggested any such concerns. (Appendix 7)

Additionally, the FDA rendered a decision through its review and approval process of Meloxicam as an Animal Medication: "The agency has determined under 21 CFR 25.33(d)(1) (Appendix 9) 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." (Appendix 10)

6. <u>Ancillary Substances:</u>

Meloxicam for oral administration was issued its US Patent in 2005 but is now past its patent protection period. Since the product is manufactured and sold by multiple manufacturers in generic form, determining a comprehensive list of all the potential ancillary substances, carriers, and excipients is not practical. However, a list of typical excipients was identified, and a link to this list is provided below, but it is possible that the list is not complete due to the numerous manufacturing sources.

Carriers/excipients:
The excipients include lactose monohydrate, microcrystalline cellulose, sodium citrate, crospovidone, povidone, colloidal anhydrous silica and magnesium stearate.
(Meloxicam Aurobindo 7.5 mg and 15 mg, tablets Aurobindo Pharma B.V., the Netherlands. PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands. 10 January 2013, (Appendix 11)

7. <u>Previous Reviews</u>:

The petitioner is not aware of any previous reviews conducted regarding this substance by the National Organic Program (NOP), the National Organic Standards Board (NOSB), a State Organic Program (SOP), or any state or private organic certification programs identified as an Accredited Certifying Agent (ACA).

8. Regulatory Authority:

Meloxicam was patented originally in 1977. The product was developed by Boerhringer Ingelheim and in 2000 it was approved for medical use. It is now available in the US in generic form. In humans, Meloxicam is a common drug prescribed for chronic pain diseases like arthritis. Meloxicam for Oral Administration received a US Patent in 2005 (US 6,869,948 B1) (Appendix 12).

An FDA website search for Meloxicam resulted in finding a New Animal Drug Application (NADA) number of 141-213. Meloxicam is listed in an FDA Federal Register notice from July 8, 2003, in 21 CFR Part 520 for New Animal Drugs in Section 520.1350 (Appendix 10). An FDA New Drug Application (NDA) number from 2000 for Meloxicam , as a human drug in a tablet form is 20-938.

These are a plethora of FDA Registration numbers in the National Drug Code (NDC) Directory Database for Meloxicam. They can be found in the National Drug Code Database. For the form of the drug referred to in this petition, a search of the NDC Database for "Meloxicam" in the "15 mg" form, the resulting listings are shown in the Appendix (Appendix 13). From this list, the first NDC Product number listed is 43063-401. (The online database can be found at https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm.)

Since this petition is prepared by supporters and potential users of Meloxicam in certified organic livestock production, rather than manufacturers, it is possible that various manufacturers, processing alternative forms, doses, and modes of administration may have received their approval utilizing alternative registration numbers not included here.

Meloxicam is currently allowed for use in dogs for the management of pain and inflammation for diseases of arthritis since 2003. It is not for use in cats in the oral form.

AMDUCA allows extra-label prescription by veterinarians:
In 1994, Congress passed the Animal Medical Drug Use Clarification Act (AMDUCA) (Appendix 14) which authorized the FDA to allow veterinarians to prescribe drugs in an extra-label (off-label) manner. The drug must be a drug approved for human or animal use, the veterinarian must have a valid veterinarian-client relationship, in cases where the animal may suffer or the animal's health in threatened and the drug is being used for therapeutic purposes, with awareness and consideration of extended withdrawal periods for food-producing animals, and not in the families of drugs that are specifically prohibited from extra-label use.

The AMDUCA Rule is CFR §530. The rule is attached. (Appendix 15)

AMDUCA requires that the extra-label use of the drug be prescribed by a veterinarian with a valid veterinary-client relationship. Once prescribed, AMDUCA does not require that the drug be administered by a veterinarian. A prescribed drug can be administered by properly trained animal care workers on the farm, allowing the opportunity for timely application of treatment even when veterinary services are unavailable.

FDA:
The FDA publishes Full Prescribing Information on their website.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020938s024s025,021530s014s015lbl.pdf (Appendix 16)

EPA:
The United States Environmental Protection Agency (EPA) posts the following review on their official (EPA HERO) government website.
https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/7564813 (Appendix 17)

Including the following abstract (in its entirety) from 2020:

Meloxicam is a non-steroidal anti-inflammatory drug, which has a preferential inhibitory effect to cyclooxyganase-2 (COX-2). Although the drug inhibits prostaglandin synthesis, the exact mechanism of meloxicam is still unknown. This is the first study to assess the effect of meloxicam on protein glyco-oxidation as well as antioxidant activity. For this purpose, we used an in vitro model of oxidized bovine serum albumin (BSA). Glucose, fructose, ribose, glyoxal and methylglyoxal were used as glycating agents, while chloramine T was used as an oxidant. We evaluated the antioxidant properties of albumin (2,2-di-phenyl-1-picrylhydrazyl radical scavenging capacity, total antioxidant capacity and ferric reducing antioxidant power), the intensity of protein glycation (Amadori products, advanced glycation end products) and glyco-oxidation (dityrosine, kynurenine, N-formylkynurenine, tryptophan and amyloid-β) as well as the content of protein oxidation products (advanced oxidation protein products, carbonyl groups and thiol groups). We have demonstrated that meloxicam enhances the antioxidant properties of albumin and prevents the protein oxidation and glycation under the influence of various factors such as sugars, aldehydes and oxidants. Importantly, the antioxidant and anti-glycating activity is similar to that of routinely used antioxidants such as captopril, Trolox, reduced glutathione and lipoic acid as well as protein glycation inhibitors (aminoguanidine). Pleiotropic action of meloxicam may increase the effectiveness of anti-inflammatory treatment in diseases with oxidative stress etiology.

NIH:
The NIH provides the following summaries on Meloxicam:
https://pubchem.ncbi.nlm.nih.gov/compound/Meloxicam (Appendix 18)

An annotated NIH PubChem (HSDS) databank:
https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741 (Appendix 7)

Chemical Entities of Biological Interest (ChEBI) - *Meloxicam is a benzothiazine that is piroxicam in which the pyridin-2-yl group is replaced by a 5-methyl-1,3-thiazol-2-yl group. A non-steroidal anti-inflammatory drug and selective inhibitor of COX-2, it is used particularly for the management of rheumatoid arthritis. It has a role as a non-steroidal anti-inflammatory drug, an antirheumatic drug, a cyclooxygenase 2 inhibitor and an analgesic. It is a benzothiazine, a monocarboxylic acid amide and a member of 1,3-thiazoles.*

DrugBank - *Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) used to relieve various types of pain, including pain caused by musculoskeletal conditions, osteoarthritis, and rheumatoid arthritis. With a longer half-life than most other NSAIDS, it is a favorable option for those who require once-daily dosing. Meloxicam is available in oral, transdermal, and intravenous formulations. It is a preferential COX-2 inhibitor, purportedly reducing the risk of adverse gastrointestinal tract effects, however, this is a topic of controversy.*

FDA Pharm Classes - *Meloxicam is a Nonsteroidal Anti-inflammatory Drug. The mechanism of action of meloxicam is as a Cyclooxygenase Inhibitor.*

LIVERTOX - *Meloxicam is a long-acting nonsteroidal anti-inflammatory drug (NSAID) available by prescription only and used in therapy of chronic arthritis. Meloxicam has been linked to rare instances of acute, clinically apparent liver injury.*

LOTUS - *Meloxicam is a natural product found in Euglena gracilis and Apis cerana with data available.*

NCI Thesaurus (NCIt) - *Meloxicam is an oxicam derivative and a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. Unlike traditional nonselective NSAIDs, meloxicam preferentially inhibits the activity of cyclo-oxygenase II (COX-II), resulting in a decreased conversion of arachidonic acid into prostaglandin precursors. The resulting decrease in prostaglandin synthesis is responsible for the therapeutic effects of meloxicam.*

MeSH - *A benzothiazine and thiazole derivative that acts as a NSAID and cyclooxygenase-2 (COX-2) inhibitor. It is used in the treatment of RHEUMATOID ARTHRITIS; OSTEOARTHRITIS; and ANKYLOSING SPONDYLITIS.*

AMDUCA: The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (Appendix 14, Appendix 19) "permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals under certain conditions." The AMDUCA Rule is CFR Title 21 Part 530 (Appendix 15). FDA provides a concise summary of The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians (Appendix 20). Meloxicam is an allowed drug for extra-label use in animals that can be prescribed by a veterinarian under certain conditions.

International Jurisdictions:

In the European Union, Meloxicam is licensed for treatment of inflammation and both acute and chronic pain relief in dogs and for use in horses for pain associated with musculoskeletal disorders.

Meloxicam - Permitted Use in International Organic Schemes

Allowance of Meloxicam in controlled pain management settings is permitted and commonly used after disbudding in Canada and the EU. The substance also appears to be allowed per the organic regulations of Switzerland and New Zealand under veterinary supervision. Canada, EU and Switzerland have trade agreements with the US, while New Zealand and the US has a recognition agreement allowing their government to accredit certifying agents to the USDA organic standards.

Canada:

Allowed under veterinary supervision as per CGSB-32.311-2020, Table 5.3 Health Care products and production aids: Anti-inflammatories – Non-steroid anti-inflammatories such as ketoprofen. Preference shall be given to alternative products, such as those listed in Table 5.3, Botanical compounds; and Homeopathy and biotherapies. (Appendix 21)

Australia:

Permitted with written approval from certifying body + may be changing with animal welfare standardization Not listed in Annex II of Australian Certified Organic Standards

New Zealand:

At this time, in New Zealand, the Organic Law passed in 2023 and official Organic Rules have not been finalized, until then organics in NZ follow the official Technical Rules for Organic Production, Section 6.5 (Appendix 22) - Disease prevention and veterinary treatment states:

6.5.5 The use of veterinary medicinal products in organic farming shall comply with the following principles:

- (a.) Phytotherapeutic (e.g. plant extracts (excluding antibiotics), essences, etc.), homeopathic products (e.g. plant, animal or mineral substances) and trace elements and products listed in Table 3.3, Table 3.4.1 and Table 3.4.2 shall be used in preference to chemically-synthesized allopathic veterinary medicinal products or antibiotics, provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended;
- (b.) If the use of these products is not effective in combating illness or injury, and treatment is essential to avoid suffering or distress to the animals, chemically-synthesized allopathic veterinary medicinal products or antibiotics may be used under the responsibility of a veterinarian.

6.5.6 The use of chemically-synthesized allopathic veterinary medicinal products or antibiotics for preventive treatments is not permitted in animals or products for which official organic assurances are sought.

6.5.10 If animals receive more than three courses of treatment with chemically-synthesized allopathic veterinary medicinal products or antibiotics within one year, they are not eligible for official organic assurances. Products derived from them are also not eligible. This does not apply to mandatory vaccinations, treatments for parasites or any compulsory eradication schemes. Animals whose productive life cycle is less than one year may not receive more than one such course of treatment. Animals which do receive more than the allowed treatments must undergo the conversion periods in Section 6.2.3.

***EU*:**

Allowed under veterinary supervision (EU) 2018/848 Annex II.1.5.2.2 states that "disease shall be treated immediately to avoid suffering to the animal. Chemically synthesized allopathic veterinary medicinal products, including antibiotics, may be used where necessary, under strict conditions and under the responsibility of a veterinarian, where the use of phytotherapeutic, homeopathic and other products is inappropriate. Where appropriate, restrictions with respect to courses of treatment and withdrawal periods shall be defined." (Appendix 23)

***Switzerland*:**

Allowed under veterinary supervision Ordinance on Organic Farming and the Labeling of Organically Produced Plant Products and Foodstuffs states in: Article 16.3 (Appendix 24) The use of veterinary medicinal products in organic stockfarming shall comply with the following principles:

> (a) Phytotherapeutic products (e.g. plant extracts, excluding antibiotics, or plant essences), homeopathic products (e.g. plant, animal and mineral substances) and trace elements and products laid down by the Department for this purpose shall be used in preference to chemically-synthesized allopathic veterinary medicinal products or antibiotics, provided that

their therapeutic effect is shown to be effective for the species of animal and the condition for which the treatment is intended.

(b) If the use of the products listed in letter a should not prove to be effective in combating illness or injury, but treatment is essential to prevent suffering or distress to the animal, chemically-synthesized allopathic veterinary medicinal products or antibiotics may be used under the responsibility of a veterinarian.

***Japan*:**

Potentially allowed under veterinary supervision. Allowance in Veterinary practice not confirmed.

In the translated version, NSAIDs or other pain relievers are not explicitly listed but anecdotal reports suggest that there is an allowance for the use of unlisted veterinary medicines with longer withdrawal period. Organic Japanese Agricultural Standard (JAS) and Technical Criteria (website in English) states: Article 4 Part 5 Health Management (Appendix 25)

-(A) For the purpose of disease prevention, appropriate raising management is to be conducted according to the type of livestock or poultry so as to strengthen their resistance to diseases and prevent infection.

-(B) In the case that livestock or poultry suffer from any injury or disease, they are to be isolated as necessary and treated promptly. In such cases, treatment and care is to be provided so that the livestock or poultry does not suffer unnecessarily.

-(C) Do not use veterinary medicinal products unless a specific disease or health problem has occurred or is likely to occur and no other appropriate treatment or control method is available, or unless required by laws and regulations (including orders and dispositions based on the provisions of laws; the same applies hereinafter). In the case where veterinary medicinal products are used, veterinary medicinal products other than medicines requiring medical examination or antibiotics are to be used.

-(D) The use of vitamins, minerals, biological preparations for animal use or veterinary medicinal products other than parasiticides in livestock or poultry is to be for therapeutic purposes only.

-(E) Notwithstanding the criteria in (C) above, if treatment with veterinary medicinal products other than medicinal products requiring medical examination or antibiotics is not effective, medicinal products requiring medical examination or antibiotics may be used. However, in the case of any of the following, the medicinal products requiring medical examination or antibiotics may not be used for the period described in (1) or (2), respectively.

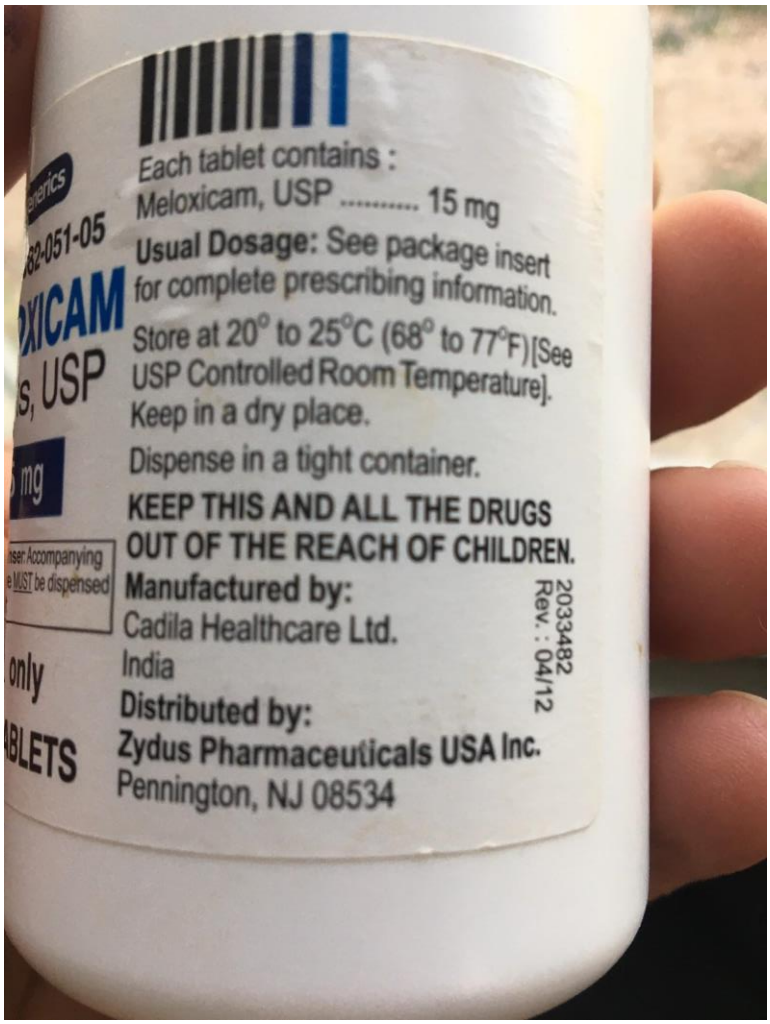
- (1) In the case of the use of any of the medicinal products listed in the column of medicinal products in Appended Table 1 and Appended Table 2 of the Ministerial Order Concerning the Regulations on the Use of Veterinary Medicinal Products (Order of the Ministry of Agriculture, Forestry and Fisheries No. 42 of 1980): A period twice as long as the period listed in the column of "Prohibited period of use" in these tables according to each category of animals listed in the column of "Animals subject to use" in these tables in accordance with the category of relevant medicinal products.
- (2) In the case of using medicinal products other than those listed in (1) above: A period of 48 hours prior to slaughtering, milking or egg collecting, or a period that is twice as long as the withholding period of drug (meaning the period from the last medication to the time of

slaughtering, milking or egg collecting) specified in the approval, modification of approved matters, reexamination or reevaluation of pharmaceuticals, etc., based on Article 14, paragraph (1), Article 14, paragraph (9), Article 14-4 and Article 14-6 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, whichever is longer.

9. <u>Chemical Abstracts Service (CAS) Number and Product Labels</u>:

CAS Number: 71125-38-7
PubChem CID: 54677470
IUPHAR/BPS: 7220
DrugBank: 7220

<u>Photos of Typical Product Labels:</u>



10. <u>Physical and Chemical Properties</u>:

Meloxicam is a cell-permeable, non-steroidal, anti-inflammatory drug (NSAID) of the oxicam family that preferentially inhibits the inducible isoform of cyclooxygenase-2 (COX-2) relative to COX-1. Also inhibits the growth of some cancer cells *in vitro*.

(a) <u>Chemical interactions with other substances, especially substances used in organic production</u>:

Meloxicam is an NSAID pain relief anti-inflammatory medication. NSAID medications can result in adverse side effects (Appendix 26) such as indigestion, stomach ulcers, headaches, drowsiness, dizziness, and allergic reactions and in rare cases problems with the liver, kidney, or heart. Meloxicam combined with other NSAIDs and possibly other related compounds could increase the risk of these adverse effects. In the case of organic livestock production these products would include aspirin or possibly natural remedies of Salicylates such as white willow bark.

(b) <u>Toxicity and environmental persistence</u>:

Toxicity and side effects:

A review of Meloxicam toxicity by the American College of Veterinary Pharmacists (ACVP) published online (Appendix 27) reports that doses greater than 5 times the therapeutic dose can result in toxicity, and that in some animals chronic use may cause toxicity. Meloxicam in the oral form is not recommended for cats. Signs and symptoms of toxicity include "vomiting, abdominal pain, melena (black, tarry stool), diarrhea. These signs may occur within an hour of ingestion. Weakness, involuntary muscle movements, and seizures may also occur, and these are signs of severe toxicity. More severe toxicity (GI perforation or renal failure) may not occur until 48-72 hours after ingestion. Signs of kidney damage include increased thirst, increased urination, loss of appetite or refusal to eat, fatigue, and vomiting." Meloxicam is not recommended in the last trimester of pregnancy.

A toxicology review in the journal InflammoPharmacology (Appendix 28) concluded that "Toxicological testing of meloxicam in animals suggests that acute oral overdosage is unlikely to cause severe toxicity in man."

Animal-excreted metabolic waste in the environment:

In the oral tablet form, the environmental persistence would be primarily from improperly disposed of product.

In the animal, after the drug has been administered, Meloxicam is metabolized to four biologically inactive metabolites and excreted in the feces and urine, suggesting that no untoward residual environmental concerns are likely to arise from this pathway. (Appendix 26)

(c) <u>Environmental impacts from its use and/or manufacture</u>:

Manufacture:

Use: As noted above, In the oral tablet form, the environmental persistence is unlikely but in the rare case would be primarily from improperly disposed of product, as is true for most medications targeting human or animal use. After the drug has been administered to the animal, Meloxicam is metabolized to four biologically inactive metabolites and excreted in the feces and urine. The consensus of available information is that with labeled use, no untoward impacts on the environment are to be expected. (Appendix 26)

Waste products:

As noted above, after the drug has been administered, Meloxicam is metabolized to four biologically inactive metabolites and excreted in the feces and urine. (Appendix 26)

(d) <u>Effects on human health</u>:

Meloxicam is an approved drug for human use. It is available by prescription and not available over the counter. It should be taken according to the recommendation of a patient's physician. A toxicology review in the journal InflammoPharmacology concluded that "Toxicological testing of meloxicam in animals suggests that acute oral overdosage is unlikely to cause severe toxicity in

man." The consensus of available information is that with labeled use, no untoward impacts on human health are to be expected.
(Appendix 28)

(e) Effects on soil organisms, crops, or livestock:

Potential effects-soil organisms: None is known nor expected. In the animal, after the drug has been administered, Meloxicam is metabolized to four biologically inactive metabolites and excreted in the feces and urine (Appendix 26).

Potential effects-crops: None is known nor expected. In the animal, after the drug has been administered, Meloxicam is metabolized to four biologically inactive metabolites and excreted in the feces and urine (Appendix 26).

Potential effects-other livestock: The only known precautions are that the oral form of Meloxicam is not recommended for cats, and it is not recommended for use in the last third of gestation.

Potential effects-aquatic: None are known or expected. In the animal, after the drug has been administered, Meloxicam is metabolized to four biologically inactive metabolites and excreted in the feces and urine (Appendix 26).

11. Safety Information:

Meloxicam is an approved drug for humans and dogs. It is a drug allowed for use in other livestock species in the US according to FDA regulations established under AMDUCA. It is considered safe in most situations, but it is not recommended during the last third trimester of pregnancy in humans nor in the oral form for cats.

Meloxicam MSDS are attached (Appendix 29).

As stated above, FDA publishes Full Prescribing Information for meloxicam on their website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020938s024s025,021530s014s015lbl.pdf The detailed report is attached (Appendix 16).

12. Research Information:

Available research findings are consistent in their noting that additional, effective Livestock Pain Management options are needed for certified organic livestock production.

Traditionally, all livestock operators have been concerned about the pain and suffering of their animals. However, as with human healthcare where pain management might have included a shot of whiskey and biting down on a stick, the tools for adequate pain management have often been deficient, for humans or for the animals under our care. Over the years, some partial remedies and tinctures were developed, and they may have been helpful to some extent. Research on those alternatives have been shown to be insufficient in many cases, short lasting, inconsistent, or provide unpredictable efficacy.

Research studies done through the Department of Animal Science at the University of Minnesota, published in 2021 and 2022, showed that both analgesic remedies, accepted as adequate pain

management historically, and natural brand-name pain relief remedies did not produce a suitable level of analgesia in calves and that additional analgesics may be required for adequate pain management. (Appendix 1, Appendix 2)

The same team of Professor B.J. Heins and graduate student Hanna N. Phillips in 2022 published in the journal Animals, a review on "Alternative Practices in Organic Dairy Production and Effects on Animal Behavior, Health, and Welfare" (Appendix 3). Summarizing the studies on the topic, they reported that pain management is one of the components of an animal's life that contributes to the animal's welfare and well-being and should be prioritized by operators.

Meloxicam research:
Meloxicam was studied extensively in humans and animal models to establish its characterization as a COX-2 NSAID, its dosage rates, and circulating and tissue half-life of the drug and length of therapeutic effect for effectiveness and dosage rate and time.

Research studies dealing more directly with meloxicam efficacy in the mitigation of pain:

Reedman, et al., reviewed the "Role of pain mitigation on the welfare of dairy calves undergoing debudding" (Appendix 30). Published in the Journal of Dairy Science in 2022, they noted that the use of local anesthetic and NSAID improve welfare outcomes in the young calves.

Winder, et al., examined the "Effects of local anesthetic or systemic analgesia on pain associated with cautery disbudding in calves: a systemic review and meta-analysis" (Appendix 31) published in the Journal of Dairy Science in 2018. The authors "recommend use of a local anesthetic and an NSAID as best practices for pain mitigation for cautery disbudding of calves 12 weeks of age or less.

In Applied Animal Behaviour Science in 2011, Stafford and Mellor published "addressing the pain associated with disbudding and dehorning in cattle (Appendix 32) determining that "if possible, local anesthesia and better still local anesthesia plus a NSAID should be used to minimize the pain caused by [dehorning] procedures."

Reedman et.al., 2022 in the Journal of Dairy Science published "Effect of plane of nutrition and analgesic drug treatment on wound healing and pain following cautery disbudding in preweaning dairy calves" (Appendix 33) examined the impact of plane of nutrition and one or two dose treatments of Meloxicam. The study showed faster healing in the calves on the higher nutrition plane but the meloxicam treatment in the study was via injection and not directly applicable to the oral administration of meloxicam focusing on in this petition.

In the case of disbudding, 'multimodal therapy – using multiple methods to manage pain' is considered the best option. The combination of a nerve block and supportive NSAID pain relief increases procedural numbness and pain relief management post procedure.

Animal Welfare group protocols like Farmers Assuring Responsible Management (FARM Reference Manual v 4, 2020) (Appendix 4) support use of both local anesthesia via a cornual nerve block and systemic pain relief from NSAIDs, specifically listing Meloxicam as the only NSAID listed by name, for additional longer lasting pain relief.

A study from Canada (Appendix 34) evaluated the administration of meloxicam to dairy cows at calving on retain fetal membranes (RP) risk and found that meloxicam did not increase the incidence of RP membranes after calving versus untreated animals and no difference in the

incidence of other periparturient (associated with calving) diseases following calving. The study concluded that "meloxicam can be used on the day of calving in lactating cows without increasing the risk of retained fetal membranes. This study shows that Meloxicam does not have a negative impact on the risk of retained fetal membranes in dairy cows when treated at calving; however, the expected milk withdrawal time for the drug in certified organic livestock production would severely limit its use in this situation.

Contrary positions

The most common contrary positions noted in research for the use of Meloxicam for pain mitigation have been included throughout this petition. They include, but are not limited to, the common warnings of NSAIDs in general including cardiovascular risk, gastrointestinal risk, organ damage, potential hypersensitivity, drug interactions especially related to overdosing when used with other NSAIDs and various short-term morbidity effects. (Appendix 7).

Other contrary positions already addressed include that, historically, a lack of pain mitigation was used during these procedures, and opponents are now calling for ceasing these procedures, such as all forms of dehorning, where the medication offers an advantage. (Appendix 3) Prohibiting these procedures could eliminate the need for a medication like this on the NL.

Another argument is the call for increased use of polled genetics in organic bovine breeding programs. Such a requirement could be difficult to implement into federal organic regulations, and would take time over generations and many years to show a significant impact of reducing horns in the organic livestock herds.

Regarding contrary opinions specific to listing of the item on the NL, the main argument is that an alternative NSAID is listed. This argument has also been addressed in this petition noting the superior pain mitigation and therapeutic effect of meloxicam in comparison to aspirin.

13. Petition Justification Statement:

Necessity

This petition is the product of unprecedented pre-market collaboration of multiple organizations who independently and collectively concluded that the interests of optimizing humane animal care for organically managed livestock required significant action to effect positive change.

The petitioners, who are not the drug manufacturer, but certified organic farmers, organic handlers, other organic industry stakeholders, and interested individuals, believe there is overwhelming need and justification for adding **Meloxicam** on the NL **§205.603** as a synthetic substance allowed for use in organic livestock production, under the OFPA category ***Livestock parasiticides and medicines*.**

The USDA/NOP Organic Rule §205.238(c)(7) requires that the producer of an organic livestock operation must not, among other things:

> *Withhold medical treatment from a sick animal in an effort to preserve its organic status. All appropriate medications must be used to restore an animal to health when methods acceptable to*

organic production fail. Livestock treated with a prohibited substance must be clearly identified and shall not be sold, labeled, or represented as organically produced.

The objective of this petition is to minimally augment the National List to provide organic livestock operators with an essential and effective means of providing conscientious pain management and make Meloxicam acceptable in organic livestock production. This would be providing not only a reasonable pain management tool to operators but doing so at a time of financial hardship for many organic livestock operations.

It is the utmost concern and responsibility for conscientious livestock operation operators to minimize and control the incidence of pain in the livestock for which they are stewards and to actively participate in the pain management of those animals through incidents of animal welfare or veterinary procedures, injury, accident, or disease. This is true for both the conventional and the certified organic livestock sector.

While certified animal welfare programs are increasingly becoming a standard bearer for animal welfare standards of livestock, those programs cannot overshadow the laws and regulations of Federal agencies such as FDA and The United States Department of Agriculture (USDA) for determining the legal framework for use of many of those practices and drugs.

While all drug approval is under the authority of the FDA, it is the USDA and the NOP that allows for the use of those legally authorized drugs within certified organic livestock production. And, while, the very nature of the NOP and the certified organic industry is that not all aspects, substances, and drugs in conventional use are valid participants within the philosophy of organic agriculture and handling in general and organic livestock in particular, any pain mitigation management tools, especially drugs, need to be considered by the organic industry, the NOP, and the NOSB to assure that certified organic livestock are not left behind those in the conventional sector and left to suffer from pain unnecessarily.

Meloxicam is not entirely different from other approved and allowed pain management substances available for use by certified organic livestock producers; however, Meloxicam is more effective, especially when compared to the efficacy of nonsynthetic tinctures and remedies. Meloxicam, in most cases, is easier to administer and less invasive to the animal than existing organic options and has longer lasting effects. Accordingly, Meloxicam could become a preferred treatment for procedures, including but not limited to, all forms of dehorning, castration, as well as musculoskeletal conditions such as lameness or arthritis.

One of the primary use cases where Meloxicam would be most effective and necessary is in disbudding or debudding in young calves. When that procedure is performed, Meloxicam is becoming the preferential medication for pain relief on conventional dairy operations, and it should be in the organic livestock producer's toolbox as well.

While portions of the certified organic industry might believe that alternative cultural methods such as leaving horned animals to grow their horns or the encouragement and emphasis of polled genetics alternatives should be preferential, the fact is that neither of these alternatives are viable alternatives as a federal policy at this point in time. Leaving horned animals to grow their horns naturally adds risk to the welfare of other animals in the herd and of the workers taking care of those animals. On the genetics side, the pool of genetics that would create a polled certified organic national herd would stifle production efficiency, operator profitability, reduce genetic progress toward genetics related to the cow as a robust and healthy harvester during the grazing season and

on pasture-based operation, and potentially increase the risk of undesirable recessive traits to establish themselves with the organic livestock herd population through in-breeding. Because the pool of polled dairy cattle is small it would take a long time before all organic cattle are polled. Therefore, it is prudent to optimize pain control until polled genetics are more widely integrated.

The use of Meloxicam is predominantly in oral tablet form providing a longer therapeutic effect between necessary treatments than current organically acceptable alternatives. As a pain medication, Meloxicam has been shown to be effective and with fewer necessary treatments imposed on the animal, its use will decrease additional stress being imposed when compared with other pain relief medications on the National List which need to be administered more frequently. Less treatment-induced stress will help animals, in most cases, particularly young calves, to recover more quickly and more efficiently, reducing overall stress.

Appendices

Appendix 1: Effects of oral white willow bark (*Salix alba*) and intravenous flunixin meglumine on prostaglandin E2 in healthy dairy calves (Phillips *et al*, 2022)

Appendix 2: Evaluation of an herbal therapy to alleviate acute pain and stress of disbudded dairy calves under organic management (Phillips and Heins, 2021)

Appendix 3: Alternative Practices in Organic Dairy Production and Effects on Animal Behavior, Health and Welfare (Phillips and Heins, 2022)

Appendix 4: FARM: Animal Care, Reference Manual Version 4 2020-2022

Appendix 5: United States National Residue Program for Meat, Poultry, and Egg Products, FY 2016 Residue Sample Results

Appendix 6: Warning Letter – Yippee Farms, LLC, May 5, 2022

Appendix 7: Meloxicam – National Library of Medicine, Hazardous Substances Data Bank (HSDB)

Appendix 8: Methyl chloroacetate – ChemicalBook-CAS DataBase List

Appendix 9: 21 CFR 25.33 Animal drugs

Appendix 10: Federal Register – Final Rule – 21 CFR Part 520 Oral Dosage Form New Animal Drugs; Meloxicam. July 21, 2003

Appendix 11: Public Assessment Report of the Medicines Evaluation Board in the Netherlands, Meloxicam Aurobindo 7.5 mg and 15 mg, tablets

Appendix 12: United States Patent No. US 6,869,948B1 – Meloxicam for Oral Administration

Appendix 13: National Drug Code Directory – Meloxicam 15 mg

Appendix 14: Animal Medicinal Drug Use Clarification Act of 1994

Appendix 15: 21 CFR 530 Extralabel Drug Use in Animals

Appendix 16: Meloxicam FDA Prescribing Information

Appendix 17: EPA HERO ID – Meloxicam

Appendix 18: National Library of Medicine Compound Summary – Meloxicam

Appendix 19: FDA.gov - Animal Medicinal Drug Use Clarification Act of 1994

Appendix 20: The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians

Appendices
(continued)

Appendix 21: National Standard of Canada/Canadian General Standards Board, CAN/CGSB-32.311-2020, Table 5.3–Health care products and production aids

Appendix 22: New Zealand Ministry of Agriculture and Forestry – Technical Rules for Organic Production, MAF Standard OP3, Appendix Two

Appendix 23: Regulation (EU) 2018-848 of the European Parliament and of the Council on organic production and labelling of organic products

Appendix 24: Switzerland – Ordinance on Organic Farming and the Labelling of Organically Produced Products and Foodstuffs, Chapter 2 Requirements for Organic Production, Section 4 Livestock Production

Appendix 25: Japanese Agricultural Standards for Organic Livestock Products, Article 4 The criteria for raising and production methods of organic livestock products

Appendix 26: National Health Service – NSAIDs

Appendix 27: American College of Veterinary Pharmacists – Meloxicam

Appendix 28: Meloxicam: A toxicology overview (Lehmann *et al*, 1996)

Appendix 29: Meloxicam Safety Data Sheet

Appendix 30: Role of pain mitigation on the welfare of dairy calves undergoing disbudding (Reedman *et al*, 2022)

Appendix 31: Effects of local anesthetic or systemic analgesia on pain associated with cautery disbudding in calves: A systematic review and meta-analysis (Winder *et al*, 2018)

Appendix 32: Addressing the pain associated with disbudding and dehorning in cattle (Stafford and Mellor, 2011)

Appendix 33: Effect of plane of nutrition and analgesic drug treatment on wound healing and pain following cautery disbudding in preweaning dairy calves (Reedman *et al*, 2022)

Appendix 34: Evaluation of the effects of treating dairy cows with meloxicam at calving on retained fetal membranes risk (Newby *et al*, 2014)

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Appendix 1

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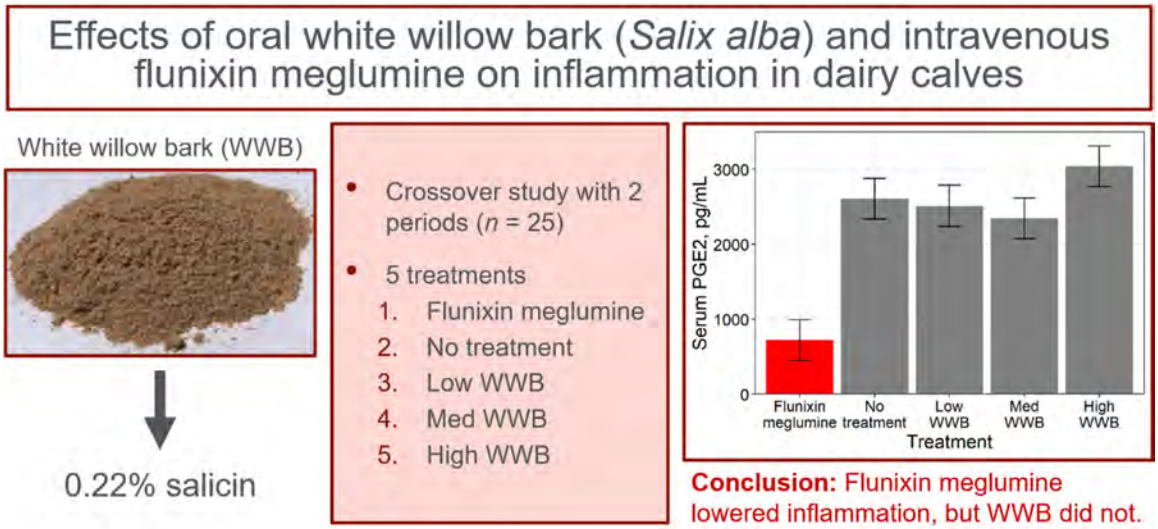
Short Communication
Health, Behavior, and Well-being

Effects of oral white willow bark (*Salix alba*) and intravenous flunixin meglumine on prostaglandin E_2 in healthy dairy calves

H. N. Phillips,[1]* K. T. Sharpe,[2] M. I. Endres,[1] and B. J. Heins[1]*

Graphical Abstract



Summary

White willow bark is a useful analgesic in humans, and its utility to alleviate pain in organic calves remains of interest. The objectives of this study were to (1) determine the salicin concentrations of non-standardized white willow bark products, and (2) to investigate the effects of intravenous flunixin meglumine and 3 oral doses (low, medium, and high) of white willow bark on the blood plasma concentrations of the inflammatory biomarker prostaglandin E2 and salicylic acid in healthy calves. The white willow bark product had 2,171 μg/g (0.22%) salicin. Flunixin meglumine lowered prostaglandin E2 (PGE_2), whereas the white willow bark doses were ineffective at reducing PGE_2 and achieving a minimum plasma salicylic acid concentration necessary for analgesia in calves. Results indicate that the white willow bark doses used in this experiment are unsuitable for producing analgesia in calves.

Highlights

- Nonstandardized products with white willow bark had a minute amount of salicin.
- Flunixin meglumine lowered the level of inflammatory biomarker.
- White willow bark did not affect the level of inflammatory biomarker.
- White willow bark did not achieve the salicylic acid concentration needed for analgesia.

[1]Department of Animal Science, University of Minnesota, St. Paul 55108, [2]West Central Research and Outreach Center, Morris, MN 56267. *Corresponding authors: phil1149@umn.edu and hein0106@umn.edu. Received June 10, 2021. Accepted September 08, 2021.

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H. N. Phillips,[1]* K. T. Sharpe,[2] M. I. Endres,[1] and B. J. Heins[1]*

Abstract: White willow bark (WWB) is commonly used in combination with other medicinal herbs and analgesics to alleviate inflammatory pain in disbudded calves under organic management, but there is no evidence to confirm an effect of WWB on inflammatory biomarkers in calves. The objective of this study was to determine whether WWB affects the inflammatory biomarker prostaglandin E_2 (PGE_2) in healthy dairy calves. A randomized crossover trial with 2 periods and 5 treatments was used for this experiment. A 7-d washout period was used to minimize carryover effects. The treatments were (1) 57.6 mg/kg oral WWB (low dose; L-WWB), (2) 115.1 mg/kg oral WWB (medium dose; M-WWB), (3) 230.3 mg/kg oral WWB (high dose; H-WWB), (4) 2.2 mg/kg i.v. flunixin meglumine (FM), or (5) no treatment (NT). Calves (n = 25) were randomly assigned to receive 1 of the 25 treatment sequences. Blood samples were collected at 1, 2, and 4 h after administration to determine PGE_2 and salicylic acid plasma concentrations. The WWB had 2,171 μg/g (± 4.3% relative standard error) salicin (0.22%). On average, calves in the FM (721 ± 274 pg/mL) treatment had lower PGE_2 than calves in all other treatments. Calves in the NT (2,606 ± 271 pg/mL), L-WWB (2,509 ± 276 pg/mL), M-WWB (2,343 ± 270 pg/mL), and H-WWB (3,039 ± 270 pg/mL) treatments had similar PGE_2 averaged across sampling times. Calves in the L-WWB (23.4 ± 1.9 ng/mL), M-WWB (21.5 ± 1.9 ng/mL), and H-WWB (23.3 ± 1.9 ng/mL) treatments had similar maximum salicylic acid plasma concentrations. Results from this study indicate that the WWB doses used in this experiment were ineffective at achieving dose-dependent PGE_2 and salicylic acid plasma concentration responses.

Dairy calves commonly experience painful disbudding procedures as part of the standard of care. According to Urie et al. (2018), approximately half (52%) of preweaning dairy calves are disbudded, but only 28% of disbudded calves are given pain mitigation therapies for the procedure. Furthermore, a survey of 189 organic dairies in the United States indicated that only 26% use a local analgesic, nonsteroidal anti-inflammatory drug (**NSAID**), or sedation to relieve pain related to horn removal procedures (Bergman et al., 2014). Organic-approved options for pain management are limited to substances approved by the USDA National Organic Program, such as flunixin meglumine (Code of Federal Regulations, 2021). However, even those permitted by the National Organic Program face barriers to common use, such as opposition by farmers, difficulty in administering, and a lack of Food and Drug Administration (**FDA**) approval for use in cattle. Despite this reluctance to implement pain alleviation methods, some organic farmers have expressed interest in or currently implement plant-based alternatives (Pol and Ruegg, 2007; Bergman et al., 2014).

An herbal tincture (Dull It, Dr. Paul's Lab) composed of ethanol, apple cider vinegar, white willow (*Salix alba*) bark, St. John's wort (*Hypericum perforatum*), chamomile (*Matricaria recutita*), arnica (*Arnica montana*), and fennel (*Foeniculum vulgare*) is currently used by many organic dairy producers as a therapy to mitigate disbudding pain and stress. However, the use of this tincture as a drug has not been approved by the FDA and is therefore is not approved for use. The herbal tincture was recently investigated as a therapy for modulating acute cautery disbudding pain in calves, in which the results indicated that the herbal tincture did not reduce the cortisol response but did reduce the behavioral response after disbudding compared with a lidocaine cornual nerve block (Phillips and Heins, 2021). To determine the possible mechanisms underlying the effect of this herbal tincture and other herbal therapies, single constituents of plants and their mechanisms should be investigated further.

Historically, white willow bark (**WWB**) has been used as an anti-inflammatory and analgesic, dating back to ancient civilizations (Maroon et al., 2010). Today, WWB is commonly used to treat painful conditions in humans (Chrubasik et al., 2000; Schmid et al., 2001b; Uehleke et al., 2013). As with all plants in the *Salix* genus, WWB contains salicylate compounds primarily composed of salicin (Kammerer et al., 2005), which is converted to salicylic acid (**SA**) in the body when consumed orally (Mahdi, 2014). Salicylic acid has anti-inflammatory effects similar to synthetic salicylates, such as acetylsalicylic acid (i.e., aspirin) and sodium salicylate, in that it inhibits cyclooxygenases and prevents the formation of prostaglandins and reduces inflammation (Amann and Peskar, 2002; Drummond et al., 2013). However, the authors are not aware of any peer-reviewed published studies indicating the usefulness of WWB for alleviating disbudding pain in calves.

Synthetic salicylates, such as aspirin and sodium salicylate, have historically been used as anti-inflammatories, antipyretics, and analgesics in cattle. Sodium salicylate administered i.v. at 50 mg/kg reduced cortisol concentrations compared with no treatment in cattle following castration (Coetzee et al., 2007). However, aspirin

[1]Department of Animal Science, University of Minnesota, St. Paul 55108, [2]West Central Research and Outreach Center, Morris, MN 56267. *Corresponding authors: phil1149@umn.edu and hein0106@umn.edu. Received June 10, 2021. Accepted September 08, 2021.

administered orally at 50 mg/kg did not attenuate cortisol (Coetzee et al., 2007). Sodium salicylate dissolved in ad libitum drinking water at rates of 2.5 to 5.0 mg/mL 1 d before and 2 d after castration and dehorning was associated with improved ADG for 13 d and decreased cortisol concentrations for up to 6 h following the procedures compared with calves that received no treatment (Baldridge et al., 2011). Yet despite the historical use of salicylates with cattle, they have never been formally approved by the FDA. Furthermore, unapproved products are currently marketed as if they are approved by the FDA and have undergone clinical research. In general, the leaves and bark of *Salix* spp. are considered safe for livestock consumption (Masika and Afolayan, 2003; Moore et al., 2003). However, the effectiveness of WWB as a pain mitigation method in dairy calves is currently lacking scientific support. Therefore, the objectives of this study were (1) to determine the salicin concentration of nonstandardized products containing WWB that are currently used or may be used for disbudding pain, and (2) to determine the effects of i.v. flunixin meglumine and 3 oral doses of WWB on the inflammatory biomarker prostaglandin E_2 (**PGE_2**) and salicylic acid plasma concentrations in healthy calves. The hypotheses of this study were (1) that PGE_2 plasma concentrations would differ among calves given flunixin meglumine, no treatment, and low, medium, and high doses of WWB; and (2) that maximum salicylic acid plasma concentrations would differ among calves given low, medium, and high doses of WWB.

The salicin concentrations were determined in 3 products: (1) the aforementioned herbal tincture (Dull It, Dr. Paul's Lab), (2) an ethanol-based WWB tincture (Mountain Rose Herbs), and (3) a dried WWB powder (Mountain Rose Herbs). Samples of each product were obtained from a single lot. Samples of the products were analyzed by a commercial laboratory (Eurofins EAG Materials Science, Maryland Heights, MO). Samples were prepared in duplicate and analyzed by HPLC in duplicate; therefore, 4 replicates per sample were analyzed. For sample preparation, the tinctures were diluted in 50% aqueous methanol and passed through a 0.45-µm filter, whereas the powder was suspended in 50% aqueous methanol, sonicated for 10 min, centrifuged at 1,510 × *g* for 15 min, and passed through a 0.45-µm filter. Samples were analyzed by HPLC equipped with a Zorbax SB-C18 phase column (5-µm particle size, 4.6 mm i.d. × 250 mm; Agilent) maintained at 35°C. The injection volume was set to 5 µL, and separation was performed at a flow rate of 1.0 mL/min starting with a solvent composition of 5% acetonitrile, increasing linearly to 20% over 13 min. The solvent composition was increased to 80% acetonitrile over 3 min and held at 80% for 5 min before equilibrating to 5%. Salicin was detected at excitation and emission wavelengths of 210 and 268 nm, respectively. Salicin had a retention time of 8.43 min with a peak retention time of 0.1858% relative standard deviation (**RSD**) and peak area of 1.0041% RSD. For quantitation, a 5-point calibration curve ranging between 10.44 and 100.13 µg/g was generated and had a R^2 greater than 0.99. The limit of detection was 10.44 µg/g. Quality control samples for the herbal tincture, WWB tincture, and WWB powder had salicin recoveries of 109, 101, and 93%, respectively. The average salicin concentration was greatest for the WWB powder (2,171.2 µg/g ± 4.3% RSD) compared with the herbal tincture (17.6 µg/g ± 3.2% RSD) and the WWB tincture (143.3 µg/g ± 5.0% RSD). Therefore, the WWB powder was used for objective 2.

The experiment for objective 2 was conducted at the University of Minnesota West Central Research and Outreach Center (Morris, MN) during December 2020 using 25 preweaning male calves. All procedures involving animals were approved by the University of Minnesota Institutional Animal Care and Use Committee (# 2007–38250A). Calves were either a crossbreed composed of Viking Red, Montbéliarde, and Holstein or a crossbreed composed of Jersey, Normande, and Viking Red. Calves were (mean ± SD) 56 ± 15 d of age and weighed 85.7 ± 20.7 kg upon study initiation. Calves were housed in a pen consisting of an indoor straw-bedded area (12.2 × 4.9 m) and an outdoor gravel area (10.7 × 4.9 m). Calves were fed pasteurized whole milk from an automated feeding system (CalfExpert Calf Feeder, Holm & Laue GmbH & Co KG). Calves had an 8-L daily allotment of milk in 2.4-L increments. Calves had ad libitum access to water and calf starter (18% CP).

A randomized crossover trial with 2 periods and 5 treatments was used for this experiment. A 7-d washout period was used to minimize carryover effects. The treatments were (1) low dose of WWB (**L-WWB**), (2) medium dose of WWB (**M-WWB**), (3) high dose of WWB (**H-WWB**), (4) flunixin meglumine (**FM**), or (5) no treatment (**NT**). The 25 calves (i.e., experimental units) were randomly assigned to receive 1 of the 25 treatment sequences. The treatment scheme is displayed in Table 1. Calves in the L-WWB, M-WWB, and H-WWB treatments received either 57.6, 115.1, or 230.3 mg of WWB powder/kg orally in boluses, corresponding to 0.125, 0.250, and 0.500 mg/kg salicin, respectively. The WWB treatments were formulated based on the salicin concentration found in the WWB powder as previously described, such that the maximum number of boluses (size 12el, 7.5-mL capacity; Torpac) administered was 5. There are no known studies that use WWB in calves. Therefore, these doses were formulated based on what was presumed to be feasible to give a calf; high doses that require numerous boluses may not be feasible for farmers based on limitations related to cost and labor. The authors agreed before the experiment that investigating doses that represent what farmers might give to their calves would be of most interest. Furthermore, this is the first experiment to investigate WWB in calves; therefore, we found it necessary to err on the side of caution to avoid giving calves potentially large and unforeseen harmful doses. The FM treatment served as the positive control for this study because FM is the only FDA- and organic-approved synthetic NSAID and it has known effects on PGE_2 concentrations in calves (Fraccaro et al., 2013). Treatment sequences were balanced, and the order of treatment was random. Calves were acclimated to handling 7 d before the study. On study days, treatment administration was staggered by 5 min. Calves in the FM group received 2.2 mg/kg i.v. flunixin meglumine (Banamine, Merck Animal Health). Calves in the NT group received no treatment. Handlers involved in collecting and processing blood samples from calves were blinded to treatments.

Blood was collected immediately before and 1, 2, and 4 h after treatment via jugular venipuncture (21-gauge × 32-mm; Vacutainer Eclipse, Becton, Dickinson and Co.). Collection times represented the periods of expected maximum SA serum concentration (1 and 2 h) and half-life (4 h) (Schmid et al., 2001a). During each sampling, blood (4 mL per tube) was collected in a sodium heparin tube (Becton, Dickinson and Co.) for PGE_2 and in a K_2 EDTA tube (Becton, Dickinson and Co.) for SA determination. Tubes were

gently inverted 8 to 10 times, immediately stored in a cooler on ice, and processed within 30 min of collection.

Sample processing for PGE_2 was as described by Allen et al. (2013). Whole blood (2 mL) was transferred from the collection tube to a 2-mL centrifuge tube (Fisher Scientific) containing 20 µL of 1 mg of LPS (Sigma-Aldrich) per 1 mL of PBS (Alfa Aesar). The centrifuge tube was inverted 3 to 5 times and incubated for 24 h in a 37°C water bath (Isotemp GPD 05, Fisher Scientific). After incubation, tubes were centrifuged (HWLAB 1–12K mini multi speed desktop centrifuge, Fristaden Lab) at 400 × *g* for 10 min before plasma was transferred to cryovials (Fisher Scientific) and frozen at −80°C. For the SA sample processing, blood was centrifuged for 15 min at 10,640 × *g* for 10 min in a chilled centrifuge (4°C), and plasma was transferred to cryovials and frozen at −80°C. Upon study completion, plasma samples were shipped overnight on dry ice to Analytical Chemistry Services (Iowa State University, Ames) for analysis.

For PGE_2 determination, protein was precipitated from samples in preparation for competitive ELISA (Cayman Chemical). In short, plasma (93.75 µL) with 375 µL of HPLC-grade methanol was centrifuged at 430 × *g*, and the supernatant was decanted into a 5-mL glass culture tube. The solvent was evaporated under a flow of nitrogen in a TurboVap LV (Biotage) at room temperature. The dried extract was resuspended in 375 µL of buffer to a dilution of 1:5. Samples were further diluted to 1:20 with buffer before analysis. Samples were analyzed in duplicate with an 8-point standard curve according to kit instructions. The assay had a detection range of 7.8 to 1,000 pg/mL. Samples were reanalyzed if the coefficient of variation was greater than 20% or if the value was not on the standard curve. Quality control samples were not run with this study, so intra-assay variability was not determined. The inter-assay variability was 10.0%. All curves were linear and had an average R^2 value of 0.99. Percent binding was 51% over all assays, and nonspecific binding was 0.29%. The limit of detection was 7.8 pg/mL, and the limit of quantitation was 9.60 pg/mL.

Table 1. Delineation of calves (n = 25) enrolled in a randomized crossover trial with 2 periods and 7-d washout by treatment sequence[1]

Calf	Period 1	Period 2
1	FM	FM
2	FM	NT
3	FM	L-WWB
4	FM	M-WWB
5	FM	H-WWB
6	NT	FM
7	NT	NT
8	NT	L-WWB
9	NT	M-WWB
10	NT	H-WWB
11	L-WWB	FM
12	L-WWB	NT
13	L-WWB	L-WWB
14	L-WWB	M-WWB
15	L-WWB	H-WWB
16	M-WWB	FM
17	M-WWB	NT
18	M-WWB	L-WWB
19	M-WWB	M-WWB
20	M-WWB	H-WWB
21	H-WWB	FM
22	H-WWB	NT
23	H-WWB	L-WWB
24	H-WWB	M-WWB
25	H-WWB	H-WWB

[1]Treatments: FM = 2.2 mg/kg i.v. flunixin meglumine; NT = no treatment; L-WWB, M-WWB, and H-WWB = 57.6, 115.1, and 230.3 mg/kg oral white willow bark in the low-, medium-, and high-dose groups, respectively.

Salicylic acid concentration was determined using methods similar to those described by Mathurkar et al. (2018). Salicylic acid concentration was determined using ultra HPLC (Thermo Vanquish Flex, Fisher Scientific) consisting of a binary pump, autosampler, column compartment, variable wavelength UV detector, and a variable wavelength fluorescence detector. Plasma (0.2 mL) was aliquoted for extraction of calibrators, quality controls, and samples. Calibrators were spiked into a blank matrix at 8 concentrations ranging from 20 to 5,000 ng/mL. Three quality control samples were spiked into blank matrices at 150, 1,500, and 3,500 ng/mL. A volume of 20 µL of 12% formic acid was added to each extraction tube, followed by 2 mL of methyl *tert*-butyl ether. Tubes were placed on a multi-tube vortex mixer for 10 min followed by centrifugation at 2,020 × *g* for 5 min at 4°C. The upper layer (1 mL) was transferred and concentrated to dryness at 25°C. Samples were reconstituted in 0.1% aqueous formic acid. The mobile phases consisted of (1) 3.5 m*M* phosphate solution with 0.1% aqueous formic acid, and (2) acetonitrile. Separation was accomplished using an aQ Accucore column (2.6-µm particle size, 2.1 mm i.d. × 100 mm; Fisher Scientific) maintained at 45°C. The autosampler was maintained at 6°C and the injection volume was set to 5 µL. The separation was performed at a flow rate of 0.3 mL/min at a starting solvent composition of 25% acetonitrile, increasing linearly to 35% acetonitrile over 3.5 min. The solvent composition was then increased to 95% acetonitrile over 0.5 min and held at 95% acetonitrile for 2 min before equilibrating to 25% acetonitrile. Salicylic acid was detected at an excitation wavelength of 295 nm and an emission wavelength of 410 nm and had a retention time of 1.92 (SD = 0.019) min. Thermo Chromeleon software (Fisher Scientific) was used to process quantitative results. A calibration consisting of 8 points between 20 and 5,000 ng/mL and a blank resulted in a linear curve with an R^2 of 0.99. The lower limit of quantification was 20 ng/mL. All quality control samples were calculated within 20% of their nominal value.

All statistical analyses used the 1.4.1103 version of the RStudio software (https://www.rstudio.com/). Analyses were performed using the *lmer* function of the *lme4* package (Bates et al., 2015). The *lmer* function fits a linear mixed-effects model. For the analysis of PGE_2, the model included fixed effects for baseline PGE_2 (continuous), BW (continuous), period (2 levels), time (3 levels), treatment (5 levels), and time × treatment interaction, and random intercepts for calf (25 levels) and calf within period to account for repeated measures (i.e., correlations between subjects). Baseline PGE_2 was analyzed in a separate model with fixed effects of BW, period, and treatment, and a random intercept for calf. For the analysis of SA, the NT and FM treatments were removed, and the maximum SA value was identified for each calf. The model for maximum SA included fixed effects for period and treatment and a random intercept for calf. Order of treatment (continuous) and breed (2 levels) were considered fixed effects candidates but were excluded from the models based on lack of improved model fit. Continuous

Table 2. Least squares means ± SEM for the effect of treatment on plasma concentrations of prostaglandin E_2 (PGE_2) and maximum salicylic acid (SA) in calves (n = 25) enrolled in a randomized crossover trial with 2 periods and 7-d washout[1]

	Treatment[2]				
Plasma concentration	FM	NT	L-WWB	M-WWB	H-WWB
PGE_2, pg/mL	721 ± 274[b]	2,606 ± 271[a]	2,509 ± 276[a]	2,343 ± 270[a]	3,039 ± 270[a]
Maximum SA, ng/mL	—	—	23.4 ± 1.9	21.5 ± 1.9	23.3 ± 1.9

[a,b]Means within a row with different letters are different at $P < 0.01$.

[1]Blood samples for determining plasma concentrations of PGE_2 and maximum SA were taken at 1, 2, and 4 h after treatment administrations.

[2]Treatments: FM = 2.2 mg/kg i.v. flunixin meglumine; NT = no treatment; L-WWB, M-WWB, and H-WWB = 57.6, 115.1, and 230.3 mg/kg oral white willow bark in the low-, medium-, and high-dose groups, respectively.

predictors were centered and scaled to have a mean of 0 and SD of 1 for all models. The REML parameter estimates were used to calculate the LSM and SEM, and *F*-tests were used to evaluate the significance of main effects. The Kenward-Roger approximation was used to calculate denominator degrees of freedom. The Tukey adjustment was applied to compare treatment means if the corresponding main effect had $P < 0.05$.

Similar baseline PGE_2 values (LSM ± SEM) were observed for calves in the FM (2,443 ± 442 pg/mL), NT (2,846 ± 444 pg/mL), L-WWB (3,170 ± 443 pg/mL), M-WWB (2,825 ± 443 pg/mL), and H-WWB (2,800 ± 441 pg/mL) treatments ($F_{4,43} = 0.3$, $P = 0.85$).

For the analysis of post-treatment PGE_2, we detected no interaction between time and treatment ($F_{8,90} = 2.0$, $P = 0.05$). However, there were effects of time ($F_{2,90} = 3.8$, $P = 0.03$) and treatment ($F_{4,37} = 11.5$, $P < 0.01$). When averaged across all post-treatment time points, calves in the FM group had lower PGE_2 compared with calves in all other treatments (Table 2). The concentration of PGE_2 (LSM ± SEM) was greater ($P = 0.03$) at 2 h (2,396 ± 164 pg/mL) than at 4 h (2,010 ± 164 pg/mL), whereas PGE_2 concentration at 1 h (2,324 ± 164 pg/mL) was intermediate compared with that at the other time points ($P \geq 0.09$).

The L-WWB, M-WWB, and H-WWB treatments had similar maximum SA (Table 2; $F_{2,7} = 1.2$, $P = 0.36$). Only 5 calves that received the WWB treatment achieved an SA plasma concentration greater than the lower limit of quantification (20 ng/mL); 4 received the H-WWB treatment and 1 received the L-WWB treatment. Maximum SA concentrations were only observed at 1 h (3 calves) and 2 h (2 calves).

This research is the first to report the use of WWB in calves. The WWB product used in this study had 2,171 µg/g (0.22%) salicin. However, the concentration of salicin may vary between lots. As expected, the FM treatment successfully reduced inflammatory mediators in calves, as indicated by lower PGE_2 values, compared with the NT treatment. However, none of the 3 doses of WWB reduced PGE_2, and the maximum SA plasma concentrations were similar among the L-WWB, M-WWB, and H-WWB treatments, indicating that the treatment doses might have been too low. Furthermore, most calves that received the WWB treatments had undetectable SA plasma concentrations, indicating that the doses of WWB were too low to detect.

Salicin is the most notable medicinal compound in WWB extracts. After ingestion, salicin is converted to metabolites in the salicylate family, which can be detected in the plasma of blood. There are several compounds that are considered salicylates, but SA is the major metabolite that makes up total salicylates detected in the plasma after ingesting salicin. In a pharmacokinetics experiment of oral WWB in humans, salicylic acid was the major metabolite (86% of total salicylates) of salicin detected in the serum (Schmid et al., 2001a). In Schmid et al. (2001a), humans with an average BW of 69.4 kg consumed a total of 1,360 mg of standardized WWB extract (240 mg of salicin) over 2 time points 3 h apart. The maximum SA plasma concentration (8.4 µmol/L) was reached after the second dose at 4 h, which was equal to 1.16 µg/mL, given the molar mass of SA (0.0084 µmol/mL × 138.121 g/mol = 1.16 µg/mL).

There are very few studies on the pharmacokinetics and pharmacodynamics of salicin. However, similar compounds, such as aspirin and sodium salicylate, also form salicylate metabolites and have been studied more intensively. The minimum total salicylate plasma concentration needed for analgesia in calves was previously estimated to be 25 to 30 µg/mL (Gingerich et al., 1975; Coetzee et al., 2007). Because SA makes up an estimated 86% of total salicylates in the plasma after consumption of salicin (Schmid et al., 2001a), the estimated minimum SA plasma concentration needed for analgesia in calves is approximately 21.5 to 25.8 µg/mL.

Previous studies of aspirin and sodium salicylate administered orally in ruminants suggest that greater doses than those used in the present experiment are needed, coupled with more frequent administration. For example, single doses of aspirin in calves (50 mg/kg) and sodium salicylate in sheep (200 mg/kg) both failed to achieve plasma salicylate concentrations above 10 µg/mL (Coetzee et al., 2007; Mathurkar et al., 2018), but aspirin at 100 mg/kg every 12 h maintained plasma salicylate concentrations above 30 µg/mL in dairy cows (Gingerich et al., 1975). Similarly, 2 daily aspirin doses of 200 mg/kg over the first 2 DIM reduced clinical metritis at 7 and 14 DIM (Barragan et al., 2021), and 3 daily sodium salicylate doses of 185 mg/kg over the first 3 DIM increased early-lactation milk yield (Carpenter et al., 2016).

The area under the curve of SA plasma concentration obtained in Schmid et al. (2001a) after humans consumed WWB extract corresponding to 240 mg of salicin (13.67 µg·h/mL) was similar to that expected after a single aspirin dose of 80 mg (12.60 µg·h/mL) and 100 mg (14.6 µg·h/mL) in humans (Benedek et al., 1995; Nagelschmitz et al., 2014). Therefore, the estimated dose of salicin can be estimated by multiplying the aspirin dose by a factor of 2.6 to 2.8. Furthermore, aspirin doses of 100, 300, and 500 mg in humans had a linearly proportional relationship with the area under the curve and maximum concentration for plasma SA (Nagelschmitz et al., 2014). Mathurkar et al. (2018) compared 2 oral doses of sodium salicylate in sheep and reported that 100 and 200 mg/kg yielded maximum SA plasma concentration values of 4.22

and 8.27 μg/mL, respectively. Based on the previous information and a linearly proportional relationship between dose and maximum concentration, calves would need sodium salicylate at a dose of approximately 520 mg/kg to reach the minimum SA plasma concentration for analgesia in calves (21.5 μg/mL). Alternatively, a total aspirin dose of 400 mg/kg given over the course of several time points may also be adequate for reducing inflammatory biomarkers (Barragan et al., 2021). After multiplying these doses by a factor of 2.6 to 2.8, the estimated dose range of salicin needed for analgesia in calves is 1,040 to 1,456 mg/kg. The dose could be given over several time points to prevent gastrointestinal upset and stress to the calves. Previous studies use maximum single aspirin and sodium salicylate doses of 200 mg/kg (Mathurkar et al., 2018; Barragan et al., 2021), so salicin doses greater than 200 mg/kg at a single time point should be administered with precaution.

The estimated amount of salicin needed to achieve analgesia in calves is quite large, considering that WWB has a minute amount of salicin. Even if a standardized WWB extract, such as a 15% salicin product, were used, it would have to be given at a total dose of approximately 6,933 to 9,707 mg/kg (equivalent to 1,040 to 1,456 mg/kg of salicin). This dose could be given over 1 to 3 d in drinking water or milk, as demonstrated with aspirin and sodium salicylate in other studies (Carpenter et al., 2016; Barragan et al., 2021). However, this method may be impractical considering time and financial constraints. Furthermore, there is currently no evidentiary support for whether WWB at high doses given over several days has any effect on inflammatory biomarkers in calves. Furthermore, other constituents of WWB might be toxic and have unknown pharmacokinetics and therefore withdrawal times. In fact, sustained high doses of WWB may have negative effects on health and welfare, such as gastrointestinal upset and consequent increased inflammation, as demonstrated in adult cattle given aspirin orally (Briggs et al., 2020).

In conclusion, the results of the current experiment reveal that products containing nonstandardized WWB have a very small amount of salicin, and the necessary dose of WWB to reduce inflammatory biomarkers and achieve a SA plasma concentration required for analgesia in calves was not determined. In fact, the WWB doses evaluated in the present experiment were likely much lower than what would be required for an appropriate dose-dependent response. The proper WWB dose for analgesia in calves is untested and may have unforeseen negative effects on animal wellbeing. Further research should focus on finding a dose of WWB or salicin that achieves a SA plasma concentration necessary for analgesia in calves before testing the efficacy of WWB under farm settings.

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Notes

H. N. Phillips https://orcid.org/0000-0003-3059-5765

K. T. Sharpe https://orcid.org/0000-0002-3955-6562

M. I. Endres https://orcid.org/0000-0002-1798-3432

B. J. Heins https://orcid.org/0000-0003-2186-9082

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Evaluation of an herbal therapy to alleviate acute pain and stress of disbudded dairy calves under organic management[1]

Hannah N. Phillips[†,2] **and Bradley J. Heins**[†,‡]

[†]Department of Animal Science, University of Minnesota, Saint Paul, MN 55108, USA; and [‡]West Central Research and Outreach Center, University of Minnesota, Morris, MN 56267, USA

ABSTRACT: The objective of this experiment was to evaluate a herbal therapy used in place of standard synthetic analgesia to mitigate disbudding pain of dairy calves. For this experiment, 54 calves were randomly assigned to one of three treatments: 1) local anesthetic lidocaine given as a cornual nerve block before cautery disbudding (AD); 2) sham disbudding (SD); or 3) herbal tincture (Dull It, Dr. Paul's Lab, Mazomanie, WI) composed of white willow (*Salix alba* L.) bark, St. John's wort (*Hypericum perforatum* L.), chamomile (*Matricaria recutita* L.), arnica (*Arnica montana* L.), and fennel (*Foeniculum vulgare* Mill.) administered orally before and after cautery disbudding (TD). Behaviors were assessed during disbudding, and behaviors and blood plasma cortisol concentrations were assessed following disbudding. Tail wag, head movement, forcing ahead, and kick rates recorded during disbudding were similar among treatments. When averaged across the 360-min observation period following disbudding, injury-directed behavioral rates of head jerks, head shakes, horn bud scratches, and head rubs were greater ($P \leq 0.03$) for calves in the AD group than calves in the SD group, calves in the TD group had greater ($P < 0.01$) horn bud scratch and head rub rates compared to calves in the SD group, and calves in the AD group had a greater ($P < 0.01$) horn bud scratch rate than calves in the TD group. Calves in the AD group took 1.6 [95% confidence interval (CI) = 1.0 to 2.4, $P = 0.03$] times longer to lie down after disbudding compared to calves in the TD group. Serum cortisol concentrations were greater ($P \leq 0.01$) for calves in the TD group compared to calves in the SD group at 10, 30, and 90 min after disbudding. At 30 min after disbudding, calves in the AD group had 5.8 ng/mL (95% CI = −1.1 to 12.7 ng/mL, $P = 0.02$) greater serum cortisol compared to calves in the SD group, while calves in the TD group had 14.3 ng/mL (95% CI = 1.5 to 27.1 ng/mL, $P < 0.01$) greater serum cortisol than calves in the AD group. In conclusion, neither the local anesthetic lidocaine nor the orally administered herbal tincture attenuated both acute injury-directed behaviors and blood plasma cortisol concentrations in disbudded calves, and the tincture was clearly less effective at mitigating cortisol; therefore, additional analgesic may be required to properly manage disbudding pain effectively.

Key words: behavior, calf, cortisol, disbud, herbal medicine, pain

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[2]Corresponding author: phil1149@umn.edu

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INTRODUCTION

Cautery horn bud removal (i.e., disbudding) of young calves is a common yet painful procedure practiced on dairy farms. Pain inflicted during the cautery disbudding procedure has been previously verified by using quantitative behavioral measurements, including rates of head movements, tail wags, and vocalizations (Graf and Senn, 1999; Grøndahl-Nielsen et al., 1999; Doherty et al., 2007). Acute pain following disbudding has been documented in numerous previous studies by evaluating blood plasma/serum cortisol concentrations, and behaviors focused around the horn bud wounds, such as ear flicks, head rubs, and head shakes (Graf and Senn, 1999; Grøndahl-Nielsen et al., 1999; Faulkner and Weary, 2000; Heinrich et al., 2009; Stilwell et al., 2012; Huber et al., 2013; Stock et al., 2016). Pain following disbudding has also been previously assessed by evaluating a range of behaviors, including lying/standing, maintenance behaviors, and rumination (Grøndahl-Nielsen et al., 1999; Faulkner and Weary, 2000; Doherty et al., 2007; Stilwell et al., 2012).

Organic dairy producers have limited analgesic options for mitigating pain in dairy calves undergoing cautery disbudding. In the United States, the use of synthetic therapies for mitigating disbudding pain in organic dairy calves is restricted by regulations set forth by the U.S. Department of Agriculture (USDA) National Organic Program (NOP), which maintains official federal standards for organic production practices (USDA-AMS-NOP, 2020). Lidocaine is a commonly used synthetic substance that is approved for use in organic-certified calves and alleviates disbudding pain by providing local analgesia. Lidocaine induces a localized insensitivity in the horn bud area within 2–5 min and has a functional duration of approximately 90 min (Coetzee, 2013). Previous studies agree that lidocaine is effective at reducing escape and struggle behaviors during disbudding, acute injury-directed behaviors up to 2 h after disbudding, and acute blood plasma/serum cortisol concentrations up to 1.5–3 h after disbudding (Graf and Senn, 1999; Grøndahl-Nielsen et al., 1999; Doherty et al., 2007). However, the injection and restraint required for administering lidocaine potentially may cause pain and stress for calves (Jimenez et al., 2019), and the use of lidocaine prior to disbudding may prolong pain following the procedure (Graf and Senn, 1999; Stilwell et al., 2012). As a possible response to these shortfalls, an emerging interest in nonsynthetic alternatives for reducing disbudding pain in organic calves currently exists. In general, organic producers are familiar with using naturally derived therapies, such as herbal-based products for the treatment of mastitis in dairy cows (Pol and Ruegg, 2007). A survey of over 189 organic dairy farms in the United States reported that 21% used a naturally derived therapy as pain management for horn removal procedures as opposed to synthetic therapies (Bergman et al., 2014). Naturally derived products—which must first be approved by the farm's NOP accredited agency—may represent potential analgesic options for mitigating cautery disbudding pain in organic dairy calves, but this hypothesis must first be evaluated under experimental conditions.

Research on the efficacy of alternative therapies used in organic livestock production is needed to verify that their use indeed improves animal welfare. Disbudding represents a major animal welfare concern among industry and nonindustry stakeholders due to the pain the procedure inflicts (Robbins et al., 2015; Ventura et al., 2015). Previous surveys of over 290 organic dairy producers and veterinarians in the United States recognized that the deficit in knowledge about effective organic-approved practices jeopardizes animal welfare (O'Neill and Wells, 2013; Pereira et al., 2013). Thus, the use of ineffective alternative practices represents a major threat to organic dairy animal welfare. In a review of dairy industry changes that affect animal welfare, Barkema et al. (2015) proposed that future research should focus on identifying effective organic-approved alternative remedies. The hypothesis of this experiment was that calves receiving a local anesthetic before disbudding, an herbal tincture before disbudding, or sham disbudding with no treatment would differ in their pain responses during and after hot-iron disbudding. Therefore, the objective

of this experiment was to evaluate pain-associated behaviors and cortisol concentration of dairy calves that received either an experimental herbal tincture prior to cautery disbudding, the current standard local anesthetic procedures prior to cautery disbudding, or no treatment prior to sham disbudding.

MATERIALS AND METHODS

Animal Housing and Care

The University of Minnesota Institutional Animal Care and Use Committee approved all animal care and procedures specific to this experiment (protocol number 1508-32864A). This experiment was conducted at the University of Minnesota West Central Research and Outreach Center in Morris, MN, from May to July 2016 using 54 preweaned female calves aged from 35 to 57 d (mean ± standard deviation = 44 ± 1 d). This age range represented the approximate national average for age at disbudding on dairy operations in the United States (USDA, 2018). Calves used in this experiment were either pure Holstein or a crossbreed as described by Heins et al. (2010). Calves were housed in groups of 10 in straw-bedded pens consisting of a three-sided shelter (3.7 × 6.1 m) with an equal-sized outdoor area. Calves were fed once daily in quantities of 6 L per calf of unprocessed organic whole milk at 0800 h as described by Kienitz et al. (2017).

Beginning 10 d prior to the experiment, calves were acclimated to halter restraint and human handling by increasing their exposure to experimental conditions incrementally each day from 30 min on the first day to 8 h on the last day. During the acclimation period, handlers would periodically visit calves to touch their horn buds and neck. The pens were scheduled for disbudding on separate days when the youngest calf in the pen reached 5 wk of age and when precipitation was not anticipated. After calves were offered milk on the days of the acclimation period and on the day of the experiment, calves were secured to the perimeter fence of the outdoor portion of the pen using a halter and lead. Each calf had enough lead (0.9 m) to lie down, stand up, drink ab libitum water from a 3.8-L bucket fastened to the fence, and interact with adjacent calves that were 1.5 m apart.

Catheter Placement

Catheters were placed into the jugular vein of calves 24 h prior to disbudding. While calves were restrained in a chute equipped with a head lock (Caf-Cart, Raytec, Ephrata, PA), hair was clipped around the horn bud area and in a 12-cm band around the neck. The area of catheter placement was surgically prepared with alternating povidone-iodine and 70% isopropyl alcohol scrubs. The hypodermis of the surrounding catheter site was anesthetized by infiltrating 2 mL of 2% lidocaine (Vedco, Saint Joseph, MO). The jugular was punctured with a 14-gauge × 133-mm peripheral venous catheter (BD Angiocath, Becton Dickinson, Franklin Lakes, NJ) and the needle was removed, so only the tube remained. Bandage tape was attached to the port and adhered to the neck using super glue (Gorilla Glue, Cincinnati, OH). An interlinking 190-mm extension set (Baxter Healthcare, Deerfield, IL) was fastened to the port and secured to calves with 76-mm wide bandage tape (Elastikon, Johnson & Johnson, New Brunswick, NJ) loosely around the neck. The catheters were flushed with 3 mL of heparin saline solution containing 130 IU of heparin per milliliter of saline and capped immediately following placement and during the evening prior to the experiment.

Experimental Design

This experiment was performed as a generalized randomized complete block design. The sample size for this experiment was determined using methods described by Guo et al. (2013) and the GLIMMPSE software for repeated measures designs (Kreidler et al., 2013). Only expected results for sham disbudding (SD) and disbudding after a lidocaine cornual nerve block (AD) were used to calculate sample size. The expected means and standard deviations for key behaviors of head movements during disbudding and head shakes at 60, 120, 180, and 240 min after disbudding were from Graf and Senn (1999). The expected means and standard deviations for cortisol at 60, 180, and 360 min after disbudding were from Stilwell et al. (2012). The expected effect sizes between treatments for head movements during disbudding, average head shakes after disbudding, and average cortisol after disbudding were 1.1, 0.9, and 2.5, respectively. For the sample size calculations for head shakes and cortisol after disbudding, a LEAR model with a base correlation of 0.50 and decay rate of 0.30 was used in the GLIMMPSE online power and sample size software (https://glimmpse.samplesizeshop.org) to account for repeated measures. The estimated sample sizes needed to achieve a power >0.80 for

head movements during disbudding, head shakes after disbudding, and cortisol after disbudding were 14, 6, and 8 calves per group, respectively. The maximum required sample size from these calculations was inflated by 30% to account for any potential dropped calves (14 × 1.30 = 18). Fifty-four calves were used for this experiment. Nine calves from each of the six pens (i.e., blocks) were randomly assigned to one of three treatments: 1) local anesthetic lidocaine given as a cornual nerve block before cautery disbudding (AD; n = 18); 2) sham disbudding (SD; n = 18); or 3) oral herbal tincture (Dull It, Dr. Paul's Lab, Mazomanie, WI) administered before and after cautery disbudding (TD; n = 18). A local anesthetic was selected as a positive control treatment since this is the most widely used synthetic pain mitigation therapy used for disbudding calves on organic dairy farms, and the use of multimodal pain therapy is rarely implemented (Vasseur et al., 2010; Bergman et al., 2014). Treatments were balanced for sire breed and age (Table 1). The disbudding order within a pen was completely randomized.

Treatment Administration

Ten minutes prior to disbudding, calves were restrained in a chute equipped with a head lock directly outside of the pen. Calves in the AD group received 5 mL of 2% lidocaine per side 5 min prior to disbudding. For each side, the needle (20 gauge × 19 mm) was inserted into the depression parallel to the temporal line pointed upward midway between the eye and horn bud, then 4 mL of lidocaine was administered into the cornual nerve and 1 mL was fanned around the nerve. Calves in the SD group did not receive any analgesic therapy, and disbudding was simulated by applying an unheated cautery iron (Inline Dehorner, Guilbert Express, New York, NY) to the horn buds of the restrained calf. Calves in the TD group received 2 mL of the herbal tincture sublingually 2 min prior to disbudding and 2 mL immediately after disbudding via a syringe. One person administered the lidocaine and tincture treatments throughout the experiment. Calves in a pen were cautery or sham disbudded 15 min apart and all calves in the experiment were cautery or sham disbudded between 1000 and 1440 h. Cautery disbudding was performed using a pistol grip cautery iron fueled by a butane/propane/propene mix (Express Dehorner, Guilbert Express, New York, NY). Cautery and sham disbudding were performed by one personnel who was blind to treatments for the cautery disbudded calves.

Table 1. Distribution of calves by treatment and age, and treatment and sire breed

	Treatment[a]		
Item	AD	SD	TD
Sire breed, count			
Holstein	6	8	8
Jersey	3	2	3
Montbéliarde	2	2	2
Normande	2	1	1
Swedish Red	5	5	4
Day of age, mean ± SD	45 ± 6	44 ± 6	44 ± 6

[a]Treatments: AD = local anesthetic lidocaine 5 min prior to cautery disbudding; SD = sham disbudded; TD = oral tincture 2 min prior to and immediately after cautery disbudding.

The dose and administration instructions for the tincture were in accordance with manufacturer guidelines. The tincture was previously marketed as a therapy to mitigate pain and stress related to castration and disbudding procedures for cattle, deer, goats, and sheep. It had been approved for use by many third-party organic certification agencies and had demonstrated popularity among organic dairy farmers for disbudding purposes. The tincture is comprised of (in order of greatest to least inclusion): ethanol, apple cider vinegar, white willow (*Salix alba* L.) bark, St. John's wort (*Hypericum perforatum* L.), chamomile (*Matricaria recutita* L.), arnica (*Arnica montana* L.), and fennel (*Foeniculum vulgare* Mill.).

Data Collection

Blood was collected at baseline (10 min prior to disbudding) and 1, 30, 90, 210, and 450 min following disbudding by discarding the first 3 mL and collecting the following 3 mL of blood, which was immediately transferred to serum separation tubes (BD Vacutainer, Becton Dickinson, Franklin Lakes, NJ) and stored at 4 °C. Tubes were centrifuged and serum was collected and maintained at −40 °C until serology. Catheter patency was maintained by flushing with 3 mL of a heparin saline solution containing 13 IU of heparin per milliliter of saline after each blood collection.

Escape and struggle behaviors during disbudding were documented from audio/video recordings of calves from five pens (45 calves). A camera (iPad 3, Apple Inc., Cupertino, CA) was placed 1 m above calves to enable a full view of each calf's body during the disbudding procedure. Frequencies of tail wags, head movements, forces ahead, kicks, vocalizations, falls, and rears were counted for the duration of restraint from the moment the cautery

iron made contact with the first horn bud to the moment the cautery iron was released from the second horn bud. The duration of cauterization was also recorded.

Behaviors during and after disbudding were documented from video recordings of calves from four pens (36 calves). Two cameras were placed on opposite sides of each pen 1.5 m above the ground. For each calf, twenty-one 5-min continuous observations were performed at baseline (60, 40, and 20 min prior to disbudding) and every 20 min following disbudding over the course of a 360-min observation period. Frequencies of ear flicks, head jerks, head shakes, head rubs, oral behaviors, horn bud scratches, and transitions, and durations of standing and ruminating were hand-recorded during each observation. An ethogram for behaviors recorded in the experiment is in Table 2. The ethological evaluation of disbudded calves was intended to assess pain since behavioral adaptations can be observed in animals subjected to pain (Morton and Griffiths, 1985). Tail wagging, head movements, forcing ahead, rapid leg movements, and vocalizations are all behavioral adaptations frequently observed in ethological evaluations of calves during the cautery disbudding procedure (Graf and Senn, 1999; Caray et al., 2015), while ear flicking, exaggerated or rapid head movements, horn bud scratching, increased transitions between standing and lying, and variations in standing/lying, ruminating, and oral manipulations are all behavioral adaptations commonly recorded in ethological evaluations of calves following cautery disbudding (Grøndahl-Nielsen et al., 1999; Heinrich et al., 2010; Stilwell et al., 2012). A single treatment-blinded observer assessed and documented behaviors. Interclass correlation coefficients of behavior observations for intrareliability were >0.90.

Cortisol Analysis

Blood serum samples were shipped over night in an insulated container with frozen carbon dioxide to the Veterinary Diagnostic Laboratory (Iowa State University, Ames, IA). Samples were analyzed for cortisol (CortiCote RIA Kit, MP Biomedical, Solon, OH) in duplicate and repeated

Table 2. Ethogram of behaviors assessed before, during, and after the disbudding procedure

Behavior[a]	Description
Observations during disbudding	
Tail wag	A rapid lateral swing of the tail from one side of the body to the other
Head movement	A distinct movement of the head away from the cautery iron or upward. Not recorded during a rear or force ahead
Force ahead	A push forcefully forward
Kick	A lift and strike with a hind leg
Vocal	An oral sound, such a bellow or bawl
Fall	A complete drop to the ground or onto knees
Rear	An attempt to lift forelegs
Observations before and after disbudding	
Injury directed	
Ear flick	A rapid movement of one or both ears. Not recorded during a head shake. Recorded as a new event once ears rested for >2 s
Head jerk	An exaggerated head movement, such as a bob, jolt, or turn. Recorded as a new event once head rested for >2 s
Head shake	A rapid head tilt from side-to-side while twisting neck. Recorded as a new event when head rested for >2 s
Head rub	A back and forth movement of the head on any object. Not recorded during a horn bud scratch. Recorded as a new event when head rested for >2 s
Horn bud scratch	A connection of the top of head with a hind hoof. Recorded as a new event when hoof returned to ground
Postural	
Standing	A stance where all hoofs are on the ground. Recorded as duration
Lying	A position where the body is in contact with the ground. Recorded as duration
Transition	A shift from standing to lying or lying to standing
Appetitive	
Oral manipulation	An interaction between an object and the mouth, such as grooming or manipulation of fixture. Not recorded during rumination. Recorded as a new event when object left mouth for >2 s
Ruminating	A chewing jaw movement when calf was not feeding. Recorded as duration

[a]All behaviors are nonmutually exclusive and recorded as a frequency unless otherwise stated.

if significant differences (interassay coefficient of variation >18%) were present among duplicates. The coefficient of variation for the intra-assay variability was 17% and the coefficient of variation for the interassay variability was 13%. The limit of detection was 0.63 ng/mL.

Statistical Analyses

All data procedures and analyses were performed using version 4.0.2 of the RStudio software (R Core Team., 2020). Pretreatment baseline values were included as covariates for analyses of behaviors and cortisol evaluated after disbudding. Baselines for each behavior represented the average of the three observations performed prior to disbudding. Four missing cortisol and 43 missing behavior (ear flicks = 10, head jerks = 7, head shakes = 7, standing = 3, transitions = 3, ruminating = 6 and oral manipulations = 7) baseline values were imputed using the sample mean within pens as described by White and Thompson (2005). Six (AD = 2, SD = 3, and TD = 1) and two (AD = 1 and TD = 1) calves were removed prior to the analyses of behaviors during and after disbudding, respectively, due to incomplete observations.

Separate models were evaluated for each outcome. All models included a covariate of *age*, a fixed effect of *treatment*, and a random intercept for *pen*. Linear mixed models for the analyses of cortisol, cauterization duration, and restraint duration were performed using the *lme* function of the *nlme* package (Pinheiro et al., 2020). Generalized linear mixed models analyzed behaviors using the *glmmTMB* function of the *glmmTMB* package (Brooks et al., 2017). For the analysis of cortisol after disbudding, the natural log transformation was applied as described by Osborne (2002).

For the analyses of outcomes evaluated after disbudding, fixed effects also included the corresponding centered and scaled *baseline* value, *time*, and *treatment* × *time* interaction. Only one and two calves performed horn bud scratches and head rubs at baseline, respectively; therefore, the baseline covariate was removed for these analyses. To incorporate the dependency among observations within calf, the random intercept for *calf* was added. The heterogeneous first-order autoregressive covariance structure was used for the analysis of cortisol evaluated after disbudding to account for correlated repeated measures and heteroscedasticity among times. The first-order autoregressive covariance structure was used for the analysis of behaviors evaluated after disbudding. Prior to the analyses of behaviors evaluated after disbudding, rarely observed outcomes of head shake, oral manipulation, standing, and rumination rates were aggregated into six 15-min time intervals by taking the summation of three consecutive 5-min time points. Similarly, horn bud scratch, head rub, and transition rates were seldom observed and were, therefore, summed into a single 90-min observation prior to analyses. Latency to lie down was recorded as the time lag corresponding to the first instance that lying was observed. Models for outcomes summed over all time points excluded fixed effects of *time*, *treatment* × *time* interaction, the random intercept for *calf*, and the covariance structure. For the analyses of behaviors evaluated during disbudding, the log of the restraint duration was an offset variable. Vocalizations, falls, and rears were observed in only 10%, 2%, and 2% of calves, respectively; and these outcomes are reported using descriptive statistics. Baseline cortisol and behaviors were analyzed separately.

For the analyses of behavior rates and latency to lie down, models were first evaluated with a Poisson distribution. Model fit was assessed by performing nonparametric overdispersion and zero-inflation tests from simulated null distributions using tools of the *DHARMa* package (Hartig, 2020); overdispersion or excess zeros were deemed present when the corresponding observation to simulation ratio was >1 ($P < 0.05$). If overdispersion was present, a negative binomial distribution with linear parameterization was used and the model was reassessed (Hardin and Hilbe, 2007). If excess zeros were present, a zero-inflated model with a single zero-inflation parameter applying to all observations was added. Poisson distributions were used for analyses of head movements and forces ahead during disbudding and ear flicks, head jerks, head rubs, head shakes, horn bud scratches, and oral manipulations after disbudding. Negative binomial distributions were used for analyses of tail wags and kicks during disbudding and transition rates and latency to lie down after disbudding. The analyses of tail wags during disbudding and horn bud scratches after disbudding included a zero-inflation factor. Beta-binomial distributions were used for analyses of standing and rumination rates after disbudding.

Maximum likelihood estimates of the model parameters were used to determine least squares means. The F and Wald X^2 tests were used to test the significance of main effects for normally and nonnormally distributed outcomes, respectively. The Tukey adjustment was applied to compare groups when the corresponding main effect had P

Appendix 2

≤0.05. For behavior outcomes, least squares means and confidence intervals (CIs) were transformed to the natural scale, and incidence rate ratios were used to compare groups.

RESULTS

Behaviors During Disbudding

Cauterization and restraint durations were consistent among treatments (Table 3). Although personnel tried to achieve the same times for cauterization and restraint between treatments, the realized time the cautery iron was in contact with the horn buds (sum of right and left horn bud) was numerically greatest for calves in the SD group. The durations of cauterization and restraint were 5.9 s [standard error (SE) = ±0.7 s] and 10.8 s (SE = ±1.3 s) when averaged across treatments, respectively.

Frequencies of behaviors recorded for the duration of disbudding restraint were similar among treatments (Table 4), indicating that restraint alone was a stressful event for calves and induced escape and struggle behaviors. Vocalization, fall, and rear behaviors were rarely observed. Vocalizations were not observed for calves in the AD but were observed in 7% and 23% of calves in the TD and SD groups, respectively. Falls were only observed for calves in the TD group (7%), and rears were only observed for calves in the AD group (7%).

Table 3. Least squares means and standard errors for effect of treatment on cauterization and restraint durations of calves undergoing disbudding procedures (N = 39)

	Treatment[a]			*F*-tests and *P*-values[b]	
Outcome, s	AD (n = 13)	SD (n = 12)	TD (n = 14)	Age (df_N = 1, df_D = 31)	Treatment (df_N = 2, df_D = 31)
Cauterization	5.6 ± 0.8	6.9 ± 0.9	5.2 ± 0.8	1.7 (0.20)	2.8 (0.07)
Restraint	11.6 ± 1.5	10.8 ± 1.5	9.9 ± 1.4	0.9 (0.35)	1.0 (0.37)

df_N, numerator degrees of freedom; df_D, denominator degrees of freedom.

[a]Treatments: AD = local anesthetic lidocaine 5 min prior to cautery disbudding; SD = sham disbudded; TD = oral tincture 2 min prior to and immediately after cautery disbudding.

Behaviors After Disbudding

Table 5 reports results for behaviors categorized into injury-directed, postural, and appetitive groups evaluated during the 360-min observation period following disbudding.

Injury-directed Behaviors After Disbudding. Ear flicks, head jerks, and head shakes were the most frequently observed injury-directed behaviors. In general, injury-directed behaviors were greatest for calves in the AD and lowest for calves in the SD group, while calves in the TD group had an intermediate response.

There was a significant treatment and time interaction for the analysis of ear flicks, so means are reported in Figure 1. In general, the SD group had the lowest rate of ear flicks, while the AD and TD group had elevated ear flick rates following the disbudding procedure. There was an effect of baseline ear flicks (X^2 = 6.3, P = 0.01) such that calves that had greater ear flicks during the pretreatment period also had greater ear flicks following the disbudding procedure. The AD group had 2.9 (95% CI = 1.0 to 8.3, P = 0.04), 5.1 (95% CI = 1.4 to 19.0, P = 0.01), and 6.9 (95% CI = 1.2 to 39.1, P = 0.03) times greater ear flick rates compared to the SD group at 180, 280, and 360 min after disbudding, respectively. The TD group had 3.9 (95% CI = 1.1 to 14.0, P = 0.03) and 5.5 (95% CI = 1.4 to 22.7, P = 0.01) times greater ear flick rates compared to the SD group at 140 and 340 min after disbudding, respectively. The TD and AD groups had similar (P ≥ 0.22) ear flick rates at

Table 4. Least squares means and 95% CIs for the effect of treatment on behavior rates of calves during disbudding procedures (N = 39)

	Treatment[a]			X^2-tests and *P*-values	
Behavior, events per 10 s[b]	AD (n = 13)	SD (n = 12)	TD (n = 14)	Age (df = 1)	Treatment (df = 2)
Tail wags	12.5 [8.3, 18.9]	13.3 [8.9, 19.9]	13.6 [9.0, 20.5]	0.2 (0.65)	0.1 (0.95)
Head movements	2.9 [1.9, 3.9]	2.1 [1.3, 2.9]	1.9 [1.2, 2.7]	0.0 (0.97)	2.9 (0.23)
Forces ahead	0.3 [0.1, 0.8]	0.5 [0.2, 1.2]	0.5 [0.2, 1.1]	0.0 (0.89)	1.1 (0.56)
Kicks	0.5 [0.1, 1.5]	0.2 [0.0, 1.0]	0.3 [0.1, 1.1]	0.6 (0.45)	0.7 (0.69)

[a]Treatment: AD = local anesthetic lidocaine 5 min prior to cautery disbudding; SD = sham disbudded; TD = oral tincture 2 min prior to and immediately after cautery disbudding.

[b]Behavior rates are reported as the number of events per 10 s of restraint.

Appendix 2

Table 5. Least squares means and 95% CIs for effect of treatment on behaviors of calves during the 360-min observation period following disbudding procedures (N = 34)

	Treatment[a]			X^2-tests and P-values[b]		
Behavior	AD (n = 11)	SD (n = 12)	TD (n = 11)	Tr (df = 2)	Ti (df = 17)	Tr × Ti (df = 34)
Injury directed						
Ear flicks, events per 5 min	–	–	–	4.9 (0.09)	30.7 (0.02)	72.7 (<0.01)
Head jerks, events per 5 min	2.1 [1.2, 3.5][a]	0.9 [0.6, 1.5][b]	1.4 [0.8, 2.4][ab]	8.3 (0.02)	6.3 (0.99)	46.2 (0.08)
Head shakes, events per 15 min[c]	1.9 [1.1, 3.4][a]	0.6 [0.4, 1.1][b]	1.2 [0.7, 2.2][ab]	7.7 (0.02)	2.9 (0.72)	10.3 (0.42)
Horn bud scratches, events per 90 min[d]	17.4 [5.9, 51.2][a]	1.0 [0.2, 3.9][c]	6.8 [2.2, 21.2][b]	62.4 (<0.01)	–	–
Head rubs, events per 90 min[d]	1.8 [0.7, 4.6][a]	0.6 [0.2, 1.8][b]	2.1 [0.9, 5.2][a]	11.5 (<0.01)	–	–
Postural						
Standing, s per 15 min[c]	84 [31, 205]	90 [36, 203]	62 [21, 172]	0.8 (0.67)	3.6 (0.61)	11.4 (0.33)
Transitions, events per 90 min[c]	4.5 [2.1, 6.9]	4.2 [2.0, 6.3]	5.3 [2.7, 8.0]	0.5 (0.78)	–	–
Latency to lie down, min	32 [25, 40][a]	24 [19, 31][ab]	20 [16, 26][b]	8.0 (0.02)	–	–
Appetitive						
Ruminating, s per 15 min[c]	7 [1, 54]	36 [7, 165]	7 [1, 53]	2.8 (0.24)	3.0 (0.71)	13.7 (0.19)
Oral manipulations, events per 15 min[c]	0.4 [0.2, 0.9]	1.0 [0.5, 1.9]	0.3 [0.1, 0.8]	5.0 (0.08)	9.4 (0.09)	8.8 (0.55)

[a–c]Labeled means without a common letter within each row differ ($P \leq 0.05$).

[a]Treatment: AD = local anesthetic lidocaine 5 min prior to cautery disbudding; SD = sham disbudded; TD = oral tincture 2 min prior to and immediately after cautery disbudding.

[b]Tr = treatment; Ti = time; Tr × Ti = treatment and time interaction.

[c]Observations were aggregated into six consecutive time intervals. X^2(Ti) df = 5; X^2(Tr × Ti) df = 10.

[d]Observations were aggregated over entire observational period.

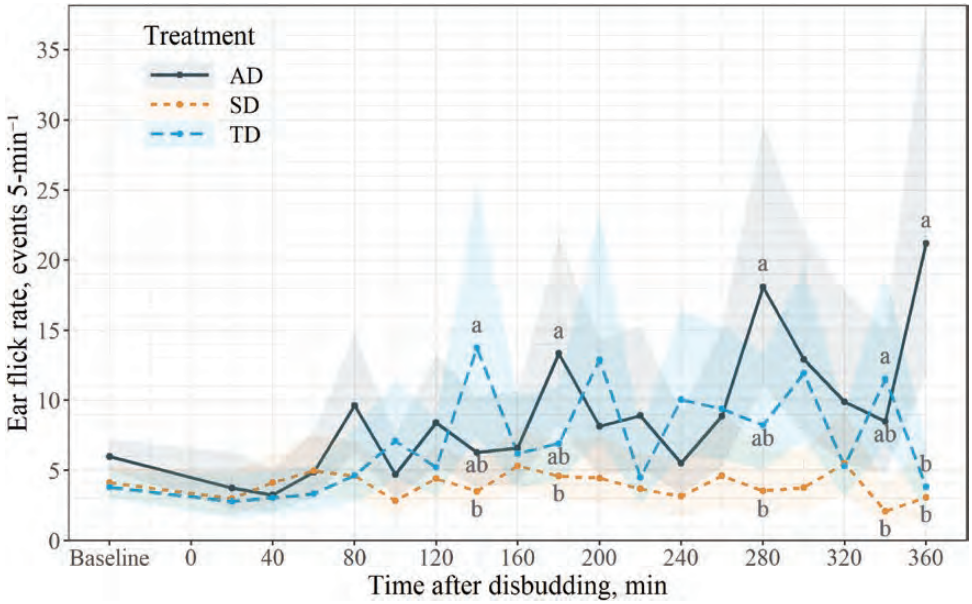

Figure 1. Least squares means and 80% CIs for interaction effect of treatment and time on ear flick rates of calves during the 360-min observation period following disbudding procedures (N = 34). The treatments were: AD = local anesthetic lidocaine 5 min prior to cautery disbudding; SD = sham disbudded; TD = oral tincture 2 min prior to and immediately after cautery disbudding. Labeled means without a common letter within each time interval differ ($P \leq 0.05$).

all time points except at 360 min after disbudding, whereas the AD group had 5.5 (95% CI = 1.4 to 22.6, P = 0.01) times the ear flick rate compared to the TD group.

The AD group had a 2.3 (95% CI = 1.1 to 4.8, P = 0.03) times greater head jerk rate than the SD group when averaged across all time points. The TD group had comparable ($P \geq 0.40$) head jerk rates to the other treatments throughout the experiment.

The AD group had a 3.0 (95% CI = 1.2 to 7.6, P = 0.01) times greater head shake rate than the SD group when averaged across all time points. The TD group had similar ($P \geq 0.24$) head shake rates to the other groups during the experiment.

Appendix 2

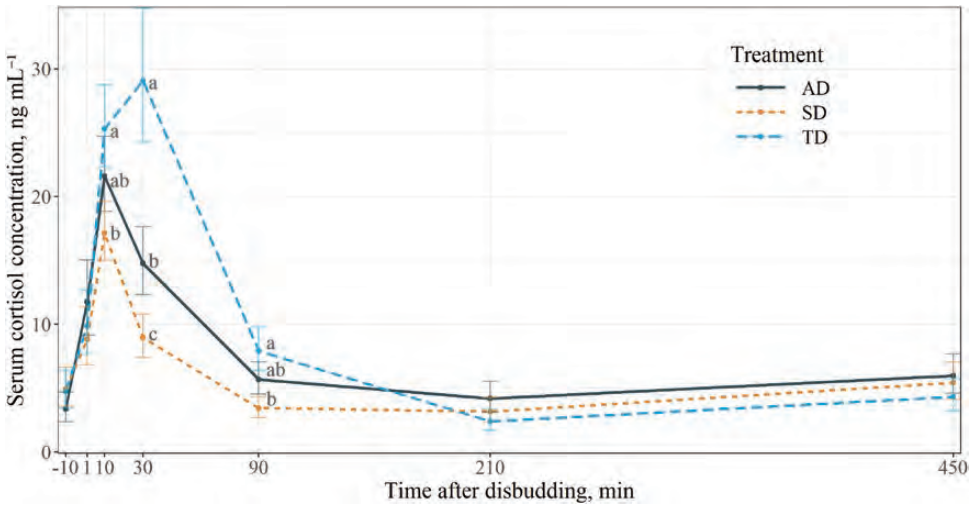

Figure 2. Least squares means and 80% CIs for interaction effect of treatment and sampling time on blood serum cortisol concentration (N = 54). The treatments were: AD = local anesthetic lidocaine 5 min prior to cautery disbudding; SD = sham disbudded; TD = oral tincture 2 min prior to and immediately after cautery disbudding. Labeled means without a common letter within each time point differ ($P \leq 0.05$).

Horn bud scratches and head rubs were the least observed injury-directed behaviors, yet calves in the AD and TD groups displayed greater ($P \leq 0.02$) frequencies compared to calves in the SD group. The AD group had the greatest horn bud scratch rate compared to the other treatments, which was 17.7 (95% CI = 6.1 to 51.4, $P < 0.01$) times greater than the SD group and 2.5 (95% CI = 1.6 to 4.2, $P < 0.01$) times greater than the TD group. Furthermore, calves in the TD scratched their horn buds at a rate that was 7.0 (95% CI = 2.2 to 21.8, $P < 0.01$) times greater than calves in the SD group. There was an effect of age on horn bud scratch rate ($X^2 = 9.4$, $P < 0.01$) such that older calves were more likely to scratch their horn buds than younger calves. Head rub rates were similar ($P = 0.86$) for disbudded calves (AD and TD) regardless of treatment. The AD and TD groups had head rub rates that were 3.0 (95% CI = 1.2 to 7.8, $P = 0.02$) and 3.5 (95% CI = 1.4 to 8.7, $P < 0.01$) times greater than the SD group.

Postural and Appetitive Behaviors After Disbudding. Standing and transition rates were similar among treatments, but calves in the AD took 1.6 (95% CI = 1.0 to 2.4, $P = 0.03$) times longer to lie down after the disbudding procedure compared to calves in the TD group. Oral manipulation rates and rumination rates were similar among treatments.

Blood Serum Cortisol

Blood serum cortisol concentrations were greater ($P < 0.01$) for the TD group compared to the SD group at 10, 30, and 90 min after disbudding and to the AD group at 30 min after disbudding (Figure 2). The effects of age, baseline cortisol, and the treatment × time interaction had $P = 0.50$, $P < 0.01$, and $P < 0.01$, respectively. There were no effects of age nor treatment for the analysis of baseline cortisol ($P \geq 0.36$). The TD group had 8.2 ng/mL (95% CI = −0.4 to 16.7 ng/mL, $P < 0.01$) greater cortisol compared to the SD group 10 min after disbudding, while the AD group had an intermediate outcome. The TD group had the greatest cortisol 30 min after disbudding, which was 20.1 ng/mL (95% CI = 8.1 to 31.1 ng/mL, $P < 0.01$) and 14.3 ng/mL (95% CI = 1.5 to 27.1 ng/mL, $P < 0.01$) greater than the SD and AD groups, respectively. The AD group also had 5.8 ng/mL (95% CI = −1.1 to 12.7 ng/mL, $P = 0.02$) greater cortisol compared to the SD group at 30 min after disbudding. The TD group had 4.5 ng/mL (95% CI = 0.4 to 8.6 ng/mL, $P < 0.01$) greater cortisol compared to the SD group 90 min after disbudding, while the AD group had an intermediate response. Furthermore, the TD and AD groups had similar ($P = 0.25$) cortisol values 90 min following disbudding.

DISCUSSION

Contrary to our hypothesis, we observed no effect of treatment on behaviors evaluated during disbudding. The relatively short cauterization duration of approximately 6 s in this experiment may explain why behavioral differences were not apparent between calves that were sham disbudded and calves that were disbudded with lidocaine but were in previous studies where the durations of

cauterization were >15 s (Graf and Senn, 1999; Grøndahl-Nielsen et al., 1999). Furthermore, the level of restraint required during the disbudding procedure may have suppressed behaviors in cautery disbudded calves. Intuitively, the handler performing the disbudding procedures was not blinded to cautery versus sham disbudding. Therefore, less restraint may have been used for sham-disbudded calves, resulting in the enhanced expression of behaviors and masking of behavioral differences between cautery and sham-disbudded calves.

In general, calves disbudded with a local anesthesia had the greatest injury-directed behavioral response after disbudding, followed by calves disbudded with the tincture and sham-disbudded calves. For the calves disbudded with a local anesthetic, head jerks and head shakes peaked at approximately 80–120 min after disbudding. This time period likely represents when sensitivity in the horn bud area returned since the functional duration of lidocaine is approximately 90 min (Coetzee, 2013). Huber et al. (2013) also reported that a greater proportion of calves displayed head shakes and horn bud scratches during the 8-h observation period following disbudding when they were administered with a local anesthetic prior to disbudding compared to sham-disbudded calves.

Sham-disbudded calves had a mean ear flick rate of 3.9 events/5 min when averaged across all time points, which is greater than previous studies that report ear flick rates of ≤1.4 events/5-min (Faulkner and Weary, 2000; Stilwell et al., 2012; Huber et al., 2013). It was unclear whether these earlier studies were performed indoors where fly populations could have been suppressed. Since the current experiment took place outdoors during the summer, fly pressure and consequent avoidance behaviors may have exacerbated ear flick rates and masked differences between treatments (Eicher and Dalley, 2002). Alas, previous studies allude that ear flick behaviors may not be a completely reliable measure of pain following disbudding such that inconsistent ear flick frequency outcomes are reported among varying levels of pain mitigation therapies (Graf and Senn, 1999; Grøndahl-Nielsen et al., 1999; Faulkner and Weary, 2000; Stilwell et al., 2012; Huber et al., 2013).

Postural behavior rates of standing, lying, and transitions were similar among treatments, but calves disbudded with the tincture were more likely to lie down compared to calves disbudded with a local anesthesia. Similarly, Faulkner and Weary (2000) reported comparable lying rates among calves disbudded with varying levels of pain mitigation therapy over a 24-h observation period, and Stilwell et al. (2012) reported no effect of pain mitigation treatment on transitions between lying and standing postures. It is unclear why calves disbudded with the tincture were more likely to lie down sooner. Perhaps the first lying instance after disbudding may reflect pain in disbudded calves, but this phenomenon is currently not supported by research. The advertised calming effects of the tincture may have resulted in recumbency immediately following the procedure, which has been previously observed in disbudded calves that received a sedative (Grøndahl-Nielsen et al., 1999; Faulkner and Weary, 2000). However, plant constituents and their physiological effects have yet to be studied extensively in cattle. Potential sedation from the tincture may actually be problematic in terms of protecting animal welfare since pain-related behaviors could be concealed without actually providing any relief from pain (Stafford et al., 2003; Stilwell et al., 2010).

Appetitive behavior rates were similar among treatments. Faulkner and Weary (2000) also reported similar grooming, feeding, and drinking rates among calves disbudded with varying levels of pain mitigation therapy. An early experiment reported that cautery disbudded calves that did not receive analgesia had decreased rumination rates during the 4-h period following disbudding and increased rumination latencies compared to calves that were not disbudded (Grøndahl-Nielsen et al., 1999). Appetitive behavior differences among treatments were negligible in the current experiment and it remains unclear whether these findings were due to the level of pain or another probable cause, such as lethargy that may have decreased behavioral responses.

Calves disbudded with the experimental tincture had the greatest cortisol response, followed by calves disbudded with the local anesthesia and sham-disbudded calves. Calves that received the tincture peaked in cortisol at 30 min, whereas the calves disbudded with the local anesthesia and sham-disbudded calves peaked at 10 min after disbudding. These results are similar to those reported by Graf and Senn (1999), where cautery disbudding without analgesia resulted in a later cortisol peak compared to sham disbudding or cautery disbudding with a local anesthetic in calves. Some previous studies reported an elevated cortisol plateau for disbudded calves that received a local anesthesia (Graf and Senn, 1999; Stilwell et al., 2012; Stock et al., 2016), but this effect was not observed in the current experiment or in another similar

experiment (Doherty et al., 2007). It is possible that a secondary peak in cortisol occurred but was not apparent due to straggling sample intervals.

Observed behaviors did not reflect the high cortisol levels for cautery disbudded calves that received the experimental tincture, which may have multiple plausible explanations. It is possible that unexpected inactivity and recumbency observed in calves that received the tincture could be partially explained by stress-induced analgesia and learned helplessness (Maier, 1984). Unusually low activity and inert behaviors have been previously documented in young animals following painful procedures as indicated in evaluations of chemically disbudded calves (Stilwell et al., 2008, 2009), cautery disbudded calves (Doherty et al., 2007), and castrated lambs (Molony et al., 1993).

The main possible plant-derived compound in the tincture includes a naturally occurring anti-inflammatory pro-drug (salicin) from willow tree (*S. alba*) bark (Mahdi, 2014), which is metabolized into salicylic acid in the body and has a similar anti-inflammatory mechanism to the nonsteroidal anti-inflammatories (NSAIDs) acetylsalicylic acid and sodium salicylate (Vane and Botting, 1998). Given the small quantity of tincture administered, it is unlikely that salicin had any pain-reduction effect on calves. According to Coetzee et al. (2007), a dose of 50 mg of oral acetylsalicylic acid per kilogram of body weight failed to attenuate peak cortisol concentrations after castration in 4- to 6-month-old cattle. Similarly, Mathurkar et al. (2018) reported that an oral dose of 200 mg of sodium salicylate per kilogram of body weight failed to achieve a level of salicylic acid in the blood plasma necessary to have any analgesia effect in 6-month-old sheep (*Ovis aries* L.). Another possible compound in the tincture is found in St. John's wort (*H. perforatum*), which is commonly used as a replacement for standard anti-depressants to treat humans with mild to moderate depression (Ng et al., 2017). The main constituents presumably responsible for the anti-depressant effects of St. John's wort are hypericin and hyperforin, yet their specific mechanisms of action are unclear and likely multifunctional (Barnes et al., 2001). Hypericin and hyperforin seem to inhibit the uptake of select neurotransmitters, such as gamma aminobutyric acid (GABA) and serotonin (Wonnemann et al., 2000). Inhibiting the uptake of GABA with gabapentin has successfully mitigated neuropathic pain in humans (Kukkar et al., 2013). Likewise, inhibiting the uptake of serotonin may mitigate acute pain as demonstrated in rodents given selective serotonin reuptake inhibitors (Singh et al., 2001; Jones et al., 2005). Few studies have investigated the analgesic effects of neurotransmitter uptake inhibitors in disbudded or dehorned calves. The combined therapy of gabapentin and the NSAID meloxicam was previously evaluated for its potential in mitigating dehorning pain in calves. While analgesic effects of the combined therapy were not outstandingly superior to other therapies, authors of these studies suggested possible synergistic pharmacokinetic properties between meloxicam and gabapentin and solicited further investigation into this phenomenon (Coetzee et al., 2011; Fraccaro et al., 2013; Glynn et al., 2013).

Regardless of the potential constituents found in the experimental tincture, numerous studies agree that systemic anti-inflammatories or opioids alone are ineffective in reducing immediate acute surgical pain on young animals as concluded under investigations with cautery disbudded calves (Caray et al., 2015), cautery disbudded goat (*Capra aegagrus hircus* L.) kids (Hempstead et al., 2020), castrated calves (Webster et al., 2013; Kleinhenz et al., 2018), and chemically disbudded calves (Stilwell et al., 2008; Braz et al., 2012; Karlen et al., 2019). Therefore, a local anesthetic should be administered to desensitize the horn bud area and effectively moderate pain during and immediately following disbudding (Grøndahl-Nielsen et al., 1999; Stilwell et al., 2008). Furthermore, when a local anesthetic is combined with a systemic NSAID, the immediate acute cortisol and injury-directed behavioral responses attenuate dramatically (Faulkner and Weary, 2000; Heinrich et al., 2009; Stilwell et al., 2012; Huber et al., 2013; Stock et al., 2016). Authors of this experiment propose that organic producers may accomplish this multimodal therapy with lidocaine as a local anesthetic and flunixin meglumine as a NSAID (Huber et al., 2013), which are both approved for use in organic livestock according to regulations set forth by the USDA-AMS-NOP (2020). Perhaps the experimental oral tincture could provide multimodal pain relief when used in combination with other validated analgesic methods, such as lidocaine; however, further evidence is required to provide any indication of its utility.

CONCLUSIONS

Authors conclude that the restraint required for disbudding alone was a stressful event for calves, and neither the local anesthetic lidocaine nor the orally administered herbal tincture eliminated acute pain in disbudded calves as suggested by observed behaviors and blood cortisol levels. Importantly, results also suggest that additional analgesic may be required to properly manage disbudding pain

effectively. The experimental tincture examined in this experiment was evidently less effective than the local anesthetic for attenuating the cortisol response following disbudding, appeared to have no mechanism to mitigate pain during the disbudding procedure, and may even suppress pain-specific behavioral responses for the hours following disbudding.

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Review

Alternative Practices in Organic Dairy Production and Effects on Animal Behavior, Health, and Welfare

Hannah N. Phillips [1,*] and Bradley J. Heins [2,*]

[1] Department of Animal Science, University of Minnesota, Saint Paul, MN 55108, USA
[2] West Central Research and Outreach Center, University of Minnesota, 46352 MN-329, Morris, MN 56267, USA
* Correspondence: phil1149@umn.edu (H.N.P.); hein0106@umn.edu (B.J.H.)

Simple Summary: The basis of livestock farming is preventing disease and improving animal welfare and well-being. Organic dairy farmers have very few options for the treatment of diseases and for the mitigation of pain in dairy calves and cows. Calving may be stressful for first-lactation cows because they must adapt to many different situations when they are milking. Alternative therapies to improve animal welfare must be researched in organic livestock production to verify that their use improves animal well-being. This review provides a brief background on organic production systems, illustrates current understanding of pain management for disbudding dairy calves, and discusses managing transition heifer behaviors and udder health to improve organic livestock well-being.

Abstract: The number of organic dairy farms has increased because of the increased growth of the organic market, higher organic milk price, and because some consumers prefer to purchase products from less intensive production systems. Best management practices are expected from organic dairy farms to ensure animal health and milk production. Organic dairy producers typically transition from conventional systems to avoid chemicals and pesticides, enhance economic viability, improve the environment, and increase soil fertility. Organic dairy producers respect and promote a natural environment for their animals, is also an important component of animal welfare. Organic producers have few options to mitigate pain in dairy calves. In the United States, therapies to mitigate pain for disbudded organic dairy calves are regulated by the US National Organic Program. Organic producers regularly use naturally derived alternatives for the treatment of health disorders of dairy calves, heifers, and cows. Alternative natural products may provide an option to mitigate pain in organic dairy calves. Despite the reluctance to implement pain alleviation methods, some organic farmers have expressed interest in or currently implement plant-based alternatives. Efficacy studies of alternative remedies for organic livestock are needed to verify that their use improves animal welfare. Non-effective practices represent a major challenge for organic dairy animal welfare. The relationship between humans and animals may be jeopardized during milking because first-lactation cows may exhibit adverse behaviors during the milking process, such as kicking and stomping. The periparturient period is particularly challenging for first-lactation cows. Adverse behaviors may jeopardize animal welfare and reduce safety for humans because stressed heifers may kick off the milking unit, kick at milkers, and display other unwanted behaviors in the milking parlor. This may reduce milking efficiency, overall production, and ultimately reduce the profitability of the dairy farm. Positive animal welfare is a challenging balancing act between the three overlapping ethic concerns. Identifying animal welfare deficits in organic livestock production is the first step in capitalizing on these opportunities to improve welfare.

Keywords: organic; behavior; disbudding; human–animal relationship

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1. Introduction

1.1. Organic Livestock Production

The history of organic agriculture provides insight to the core values of today's organic livestock industry. Agriculture polarized in the United States at the turn of the Environmental Revolution in the 1970s over concerns about chemical fertilizers and pesticides [1]. After years of organic industry groups requesting the protection of their farming practices, the US congress passed the Organic Foods Production Act of 1990, which created national standards for all aspects of organic agriculture to help unify organic practices. In 2001, the USDA created the National Organic Program (NOP) and Code of Federal Regulations (Title 7, Subtitle B, Chapter I, Subchapter M, Part 205) [2] to protect the integrity of the organic seal and mandate regulations. For example, all organic farms must undergo a certifying process by an NOP-accredited agency. Although there are several technical differences between organic and conventional livestock systems, the major defining characteristics include grazing and outdoor access requirements and the prohibition of most synthetic substances (e.g., antibiotics). The term "conventional" is an ambiguous term used to describe non-organic systems and—more than likely—intensive farming systems. However, there are some cases where these conventional, intensive, and non-organic farms may adopt some organic practices, such as grazing and alternative therapies. Henceforth, conventional is defined as "non-organic livestock systems that keep animals in total indoor confinement and have the ability to utilize treatments that are not allowed in organic practices, such as antibiotics, when necessary. Organic production systems are defined by the NOP as systems that are managed in accordance with the rules and regulations to respond to site-specific conditions by integrating cultural, biological, and mechanical practices that foster cycling of resources, promote ecological balance, and conserve biodiversity [2].

The National Organic Standards Board (NOSB), an advisory board for the NOP, reviews standards and reports recommendations to the NOP. For example, the NOSB may review and recommend the allowance of certain synthetic substances if a justified need exists and evidence supports their safety to people and the environment. If the NOP accepts the NOSB recommendations, the NOP initiates rulemaking to change The National List of Allowed and Prohibited Substances (§205.607) in the Code of Federal Regulations, which is available to the public [2]. The primary values of organic agriculture still exist in the modern organic livestock industry, and they serve as a foundation to support contemporary goals.

For health care, organic dairy producers should establish livestock health practices that focus on the prevention of disease and sickness. However, if management practices are inadequate to prevent illness, a producer may administer synthetic medications that are allowed under the NOP National List. Livestock producers should not withhold treatment from a sick animal to preserve the organic status of the animal. When methods of treatment in organic production fail, all methods must be used to restore an animal to health [2].

The organic industry is a fast-growing agricultural segment [3]. In the US, the organic livestock sector is dominated by dairy and poultry [4]. The top reported reasons why organic dairy producers choose to transition from conventional systems are to (1) avoid chemicals and pesticides, (2) enhance economic viability, and (3) improve the environment and soil [5]. These explanations expose modern motivations, yet reported themes still honor the earliest organic values of fostering natural systems.

1.2. Animal Welfare

Animal welfare is multifactorial; all components of an animal's life contribute to its overall well-being [6]. There are several definitions of animal welfare, such as Broom's 1986 definition, "The welfare of an individual is its state as regards its attempts to cope with its environment" [7]; The Five Freedoms developed between 1965 and 1979 [8,9]; and The Allostasis Concept, which appeared in 2007 [10]. Although these definitions contribute to the knowledge of animal welfare, the Fraser et al. [11] framework best describes how the organic industry values animal welfare.

In 1997, Fraser et al. [11] developed a holistic framework consisting of three overlapping ethical concerns in which animal welfare can be evaluated and human preference can be categorized (Figure 1). The framework's ethical views are: (1) animals should be sound in terms of health and physiology (i.e., biological function), (2) animals should experience natural lives (i.e., natural living), and (3) animals should be free of negative emotional states (i.e., affective state). When evaluating animal welfare, people tend to emphasize the importance of one category over the others. For example, the NOP dairy standards value systems that mimic nature and commend practices that maximize the natural lives of animals—the natural living component of the animal welfare framework. Thus, organic producers tend to value natural living more than biological functioning and affective state when considering animal welfare [12].

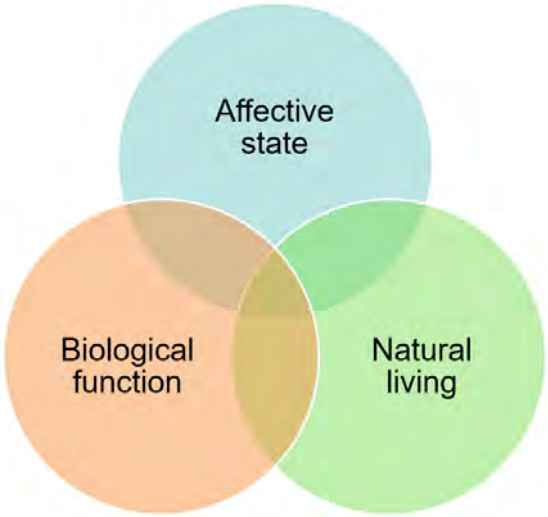

Figure 1. The animal welfare framework. Descriptions were developed by Fraser et al. [11].

Organic standards emphasize that animals should live according to nature, which may be accomplished by allowing animals to be reared with access to the outdoors, restricted periods of indoor confinement, and reduced stocking densities [13]. Animals raised organically may have more freedom to express natural behaviors compared to animals living in conventional systems. Furthermore, access to the outdoors may have an advantageous effect on animal health in some cases. In a review of literature on behavioral differences between cows housed with and without pasture access, Charlton and Rutter [14] suggested that the pasture environment may alleviate some animal health issues that are aggravated in total indoor confinement systems, such as lameness and hock lesions possibly caused by exposure to hard (e.g., concrete) flooring and resting areas. Alternatively, the pasture environment can introduce other challenges that may jeopardize animal welfare, such as biting flies [15,16], heat stress [17,18], an increase in gastrointestinal parasites [19], and impairment of the human–animal relationship [20,21] in dairy cows.

Animals living in organic systems may have some advantages for improved animal welfare compared to those raised in conventional systems, especially in terms of abilities to perform natural behaviors and alleviate animal welfare issues exacerbated by total confinement. However, the pasture environment presents its own animal welfare challenges, and there are several other facets of organic practices to deliberate upon that potentially affect animal welfare.

Placing most of the focus into the natural living component of animal welfare may be problematic for organic animals because emphasis in only one category comes at the expense of the others. To support this idea, previous literature acknowledged the deficits in organic livestock production regarding the biological function and affective state categories [22]. Bergman et al. [23] reported that organic dairy farms were less compliant compared to their conventional counterparts on the use of pain relief for disbudding calves,

which may be partially due to the limited organic-approved options for pain relief. In a survey of veterinarian perspectives of organic livestock production, Sorge et al. [24] found that many veterinarians disagreed that animal health was improved on organic farms and expressed concern for the absence of proven therapies that may impair animal welfare on farms. Furthermore, veterinarians reported they struggled to successfully treat sick animals with alternative management practices within NOP guidelines [24]. It is evident that there are many disadvantages to organic animal production systems, especially when animals require a treatment intervention and alternative therapies fail.

It is noteworthy to acknowledge that animals have preferences within their living environment. Previous studies found that dairy cows prefer pasture, which is contingent on many factors, including time of day, weather, and individual variation [14,25,26]. It seems intuitive to think that animals raised in organic systems—where the freedom of choice is allowed—have better welfare, though the opportunity for choice may not necessarily relate to improved animal welfare, as animals may not choose what is in the best interest of their welfare.

Motivation tests have been used to determine the intensity of an animal who is willing to work to acquire a resource [27]. It has been suggested that strong motivation for a resource indicates that the resource is vital to the animal and denying that resource has a negative effect on animal welfare [28]. In an experiment by von Keyserlingk et al. [29], trained dairy cows pushed open a gate to access fresh feed or pasture. Cows pushed a similar weight to acquire feed and pasture but pushed more weight to gain pasture access at night [29]. Another experiment by Charlton et al. [26] found that dairy cows' time on pasture declined when walking distance increased during the day but walking distance did not affect nighttime pasture use. Therefore, access to pasture may be an especially important resource for dairy cows at night. Therefore, the ability of an animal to access a resource that is highly important may influence animal welfare, but further research is required to verify whether having this access directly improves animal welfare.

There is currently no strong evidence on whether animals reared in organic systems have inferior or superior welfare compared with animals raised in conventional systems [30]. Furthermore, the level of animal welfare is likely contingent on various management factors and complex situations. For example, Sutherland et al. [31] reported that mastitis is a common and important welfare issue for dairy cattle regardless of organic status. While mastitis may be less common on some organic dairy farms [32], antibiotics are prohibited in organic production, so the ability to effectively treat organic cows for mastitis is limited. Ruegg [33] reported that alternative therapies—such as whey-based therapies, garlic tincture, and aloe vera—are commonly used to treat mastitis in organic cows, but limited research exists on whether these therapies are effective, and their use may actually prolong suffering. Positive animal welfare is a challenging balancing act between the three overlapping ethic concerns. Identifying animal welfare deficits in organic livestock production is the first step in capitalizing on these opportunities to improve welfare.

2. Pain Management for Disbudding

2.1. Horn Removal

Whether performed under conventional or organic management, horn removal is a major concern among the industry and the public [34,35]. However, the majority of dairy farms in the US (94%) remove horns [36]. Horns are perceived as a risk for animal and human injury and are therefore undesirable [37]. However, very little evidence has shown that horns are a risk for injury if farmers provide excellent housing and management and maintain a suitable human–cattle relationship [38]. Moreover, horn removal may have little benefit to animal and human safety [39]. At the present, there is evidence of stakeholder interest in preserving horns [34,40]. In the US, there are no current studies on horned dairy cattle, so it is difficult to accurately enumerate the presence of horned organic herds. In the European Union, a survey of 419 dairy farms estimated that 78% of organic farms had animals with horns [41]. Perhaps unaccounted horned organic dairy herds exist in the US,

especially considering current trends in the European Union. Preserving horns as a strategy to enhance dairy cattle welfare is insufficiently investigated and represents a research topic of high priority. However, horn removal is still dominant in the organic dairy sector [5,23]; thus, scientific investigation on ways to mitigate pain inflicted by horn removal procedures still demands continuation. Despite a reluctance to implement pain alleviation methods, organic dairy farmers support disbudding as an accepted practice. However, organic dairy farmers are exploring other alternatives to disbudding, such as polled genetics [42].

Dehorning is the most painful and least desired method of horn removal [43] and is defined as "The process of removing the horn of an adult cow after the horn has developed attachment to the skull" [43]. Therefore, the dairy industry has advocated for farmers to disbud calves instead [44]. Disbudding is defined as "the process of damaging the horn bud in young calves to prevent the growth of horns" [43]. Over the years, disbudding has increased in popularity as a method of horn removal, such that disbudding was implemented on 86% of dairy farms in 2014 the US. The two major methods used to disbud calves include cauterization and caustic paste [36]; however, caustic paste is generally not approved for organic use, since it contains chemicals that destroy the horn bud tissue after topical application (§205.603). Furthermore, the use of caustic paste can be problematic, since it has been demonstrated in clinical trials to cause pain and become dangerous if accidently transmitted to other body parts [45,46]. Therefore, caustic paste should be promoted with caution, since it could encourage farmers to rear calves in isolation, which has detrimental effects on animal welfare [47]. Therefore, cautery disbudding represents the primary method of horn removal in organic dairy calves and a widespread animal welfare issue for the organic sector.

Pain is the most significant acute effect of cautery disbudding. Calves exhibit intense and frequent escape behaviors during disbudding [48] and elevated pain and wound sensitivities for at least 24 h after the disbudding [49,50]. Stewart et al. [51] showed deviations in ocular temperature within minutes after disbudding, suggesting immediate pain following disbudding. Neave et al. [52] found that calves were less likely to complete an ambiguous task at 6 and 22 h after disbudding, suggesting "pessimism" in disbudded calves. Recent studies even suggest that disbudded calves experience prolonged pain before [53] and after [54] the wounds re-epithelialize, which takes approximately 9 weeks [53]. The long-term pain of disbudding is poorly understood and could have ramifications on the welfare of adult cows.

Therefore, disbudding is a major animal welfare concern with potential long-term negative effects, and strategies to minimize pain should be utilized. The NOP recommends instilling practices which minimize acute pain and stress caused by the disbudding procedure using effective methods and approved therapies. However, organic producers have limited pain mitigation therapy options (§205.238) [2], making disbudding pain management a challenge and widespread animal welfare issue for the organic sector.

2.2. Pain Management

The best way to alleviate acute disbudding pain is through multimodal therapy—using multiple methods to manage pain. In a review of 21 studies by Winder et al. [55], it was suggested that the combination of a cornual nerve block with an anesthetic and a systemic non-steroidal anti-inflammatory drug (NSAID) increases acute numbness compared to a local anesthetic alone. A local anesthetic induces numbness in the horn bud area, and the NSAID systemically reduces inflammation by inhibiting the enzyme cyclooxygenase (COX) and consequent synthesis of inflammatory prostaglandins, such as prostaglandin E2 (PGE2; [56]). This multimodal method is useful because local anesthetics have a functional duration of approximately 90 min [57], and a long-lasting NSAID may alleviate the inflammatory pain thereafter [55]. However, multimodal pain mitigation therapies are rarely implemented on organic dairy farms.

Pain alleviation methods for disbudding are quite low and depend on several factors of feasibility. A recent survey of 189 US organic dairy producers reported that less than 26%

of farms used either a local anesthetic or an NSAID for disbudding calves [23], and the use of multimodal pain therapy is estimated to be rare [58]. Organic producers are restricted to substances that are approved by the NOP (§205.603), and the few NSAID options available limit the feasibility of proper pain alleviation. For example, lidocaine (e.g., local anesthetic) and aspirin (e.g., NSAID) were added to the NOP National List of substances in 1995 and are generally acknowledged as substances that accommodate organic values [59]. However, aspirin is not approved by the Food and Drug Administration (FDA) for use in cattle and is therefore not allowed. In 2007, flunixin (e.g., NSAID) was added to The National List of Allowed and Prohibited Substances in light of its positive impact on animal welfare [59]. However, flunixin was simultaneously strongly opposed by farmers and NOSB reviewers, who were charged by its contradiction of organic values [59]. Furthermore, flunixin must be administered intravenously (i.v.), which may be a contributing factor to its lack of adoption, since i.v. methods may be challenging and unappealing to some producers [60]. Consequently, organic farmers have demonstrated reluctance to implement flunixin as a post-operative pain management therapy but have expressed interest in plant-based alternatives to alleviate pain [32]. Furthermore, xylazine is allowed for use under the USDA-NOP but must be used by or under the direction of a veterinarian (The National List of Allowed and Prohibited Substances (§205.603) [59]. In Finland, Adam et al. [61] reported that a low dose of xylazine allowed for sufficient sedation as a local anesthetic for disbudding in Finnish Ayrshire calves. However, xylazine does have a side effect of decreasing core body temperature after injection for dairy calves that were disbudded [62]. Vickers et al. [45] recommend that xylazine should be used when disbudding with caustic paste, even though xylazine does not have an anesthetic effect. Recently, calves sedated with xylazine prior to disbudding had less response to pain stimuli and greater rates of play behavior following sedation [63].

Lidocaine as a local anesthetic is approved as a cornual nerve block in organic dairy cattle. However, lidocaine use requires a withdrawal period of 6 days after administration to dairy calves that are disbudded [59]. Lidocaine 2% is a commonly used synthetic substance for organic livestock and alleviates disbudding pain by providing local analgesia [55]. Lidocaine provides analgesia the horn bud area within 2 to 5 min and has a duration of 90 min. Organic dairy producer and veterinary stakeholders have either adopted or exhibited an interest in non-synthetic substances, such as herbal therapies, to mitigate disbudding pain [23,32]. A survey of over 180 US organic dairy farms reported that a quarter of dairy farms used natural therapy as pain management for horn removal procedures [23]. However, these alternative therapies may be a problematic solution, since their efficacy is mostly based on anecdotal evidence. A survey of over 150 US organic dairy producers found reduced knowledge of farmers about effective organic-approved practices [64]. Furthermore, alternative practices have been identified as a major threat to organic dairy welfare [65]. Recently, Barkema et al. [66] proposed that future research should identify organic-approved alternative remedies that are effective for reducing pain.

Pain and stress are challenging to quantify and understand in animals. Physiological measures of pain can be useful but also require careful interpretation [49]. The body responds to pain by triggering an autonomic nervous system (ANS) response [67]. In particular, the sympathetic nervous system (SNS) of the ANS orchestrates a fight-or-flight response, in which the brain communicates to the adrenal gland via converging systems; the sympathetic–adrenal–medullary (SAM) system uses electrical signals, and the hypothalamic–pituitary–adrenal (HPA) axis uses a series of cascading hormones to prompt the adrenal gland [67]. The SAM system quickly triggers the adrenal gland to release catecholamines, such as adrenaline and norepinephrine, to increase vigilance and ultimately prepare the body for immediate physical reaction [67]. The HPA stimulates the adrenal gland to release cortisol, which may have a variety of prolonged functions, including immune and inflammatory suppression [68]. Therefore, pain and stress in animals can be inferred by observing elevated hormones involved in the SAM and HPA axis function [68].

However, the HPA axis hormones may be problematic measurements of pain since they elevate in response to other categories of stressors.

Quantifying pain-specific behaviors that increase in frequency after disbudding (e.g., ear flicks and head rubs) is another useful tool to draw conclusions about pain in disbudded calves [69]). However, as behavior measures may be inconsistent between studies, subjective, time-consuming, and variable between individual animals [55,60], it is important to examine diverse pain characteristics in examinations of disbudding pain in calves.

2.3. Alternative Non-Steroidal Anti-Inflammatory Drugs—Synthetic Salicylates

Synthetic salicylates, such as acetylsalicylic acid (i.e., aspirin) and sodium salicylate, have previously been used as effective anti-inflammatories, antipyretics, and analgesics in cattle. In an experiment by Coetzee et al. [70], intravenous sodium salicylate administered at a dose of 50 mg/kg reduced cortisol concentrations when compared to untreated cattle following castration. However, a 50 mg/kg oral dose of aspirin did not mitigate the cortisol response Coetzee, et al. [70]. In another experiment, Baldridge et al. [71] reported that sodium salicylate dissolved in ab libitum water at rates of 2.5 to 5.0 mg/mL and offered from 1 day before to 2 days after castration and dehorning improved ADG for the next 13 days and decreased cortisol concentrations for up to 6 h after the procedures compared to calves that received no treatment. Although synthetic salicylates show promising utility for pain mitigation in cattle, they have never been officially approved by the FDA and are therefore not permitted.

2.4. Alternative Non-Steroidal Anti-Inflammatory Drugs—White Willow Bark

White willow (*Salix alba* L.) bark (WWB) is one of the most popular plant-based therapies used for pain relief [72]. As with all plants from the Salix genus, white willow bark contains salicylate compounds primarily comprised of salicin [73], which is converted into salicylic acid (SA) when consumed orally [74]. Salicylic acid is similar to synthetic salicylates, such that it inhibits the enzyme COX and blocks inflammatory prostaglandins, such as PGE2 [75]. Various studies reported reductions in pain when administering WWB to humans [76,77].

White willow bark may be a useful alternative to synthetic salicylates to mitigate the delayed onset of pain in disbudded calves. Plant matter, especially leaf and branch trimmings, from the Salix genus have been previously demonstrated to be a nutritious feed source in agroforestry systems and safe for consumption by ruminants [78–81], but the efficacy of WWB as an alternative therapy to alleviate pain in cattle is currently unsupported by scientific evidence. Furthermore, animal welfare critics of the organic dairy industry constantly reference unproven alternative therapies as a major animal welfare concern [12,22,23]. Therefore, it is essential that scientific research begins filling this exposed knowledge gap by investigating WWB for its analgesic effects in calves. Recently, Phillips et al. [42] reported that white willow bark contains 0.22% salicin. For blood plasma concentrations of the inflammatory biomarker PGE2, flunixin meglumine lowered PGE2, whereas white willow bark was ineffective at reducing PGE2 and achieving the minimum salicylic acid concentration necessary for analgesia in calves. The results indicated that white willow bark provided in three oral doses was unsuitable for producing analgesia in calves [42].

Salicin is the most prominent compound in WWB extracts that is responsible for anti-inflammatory effects [82]. However, the amount of salicin in WWB products is not commonly provided by manufacturers. In an observational study to evaluate the amount of salicin in the bark of various Salix species grown in Lithuania, Kenstavičiene et al. [83] found that WWB contains 1.21 to 1.87% salicin. Furthermore, Pitta et al. [79] and McWilliam et al. [80] reported that leaf and branch trimmings from Salix species contained 0.09 to 0.17% salicin. High-performance liquid chromatography (HPLC) is the most common method of determining the concentration of salicin in plant matter. The amount of salicin in WWB products, such as ground and dried WWB powder, is not typically evaluated by manufacturers.

Therefore, the salicin concentration of several WWB products that are currently used or may be used by the organic dairy industry to mitigate pain will be evaluated using HPLC.

After ingestion, salicin is converted to several different metabolites from the salicylate family which can be detected in the plasma of blood. Salicylic acid is the major metabolite that makes up total salicylates detected in the plasma after ingesting salicin. In a pharmacokinetic experiment of oral WWB in humans, salicylic acid made up 86% of the total detected salicylates in the blood serum [84]. The minimum total salicylate plasma concentration needed for analgesia in calves was previously estimated to be 25 to 30 μg/mL [85]. Since SA makes up an estimated 86% of total salicylates in the plasma after ingesting salicin [84], the estimated minimum SA plasma concentration needed for analgesia in calves is approximately 21.5 to 25.8 μg/mL. Therefore, plasma concentrations of SA will be measured in calves receiving WWB to determine if the minimum SA plasma concentration needed for analgesia in calves is met and to corroborate inflammation findings.

Non-steroidal compounds prevent inflammation by inhibiting COX, the class of enzymes involved in the production of inflammatory prostaglandins [86]. Prostaglandin E2 is the most notable inflammatory prostaglandin because of its superior effect on the processing of pain signals [87]. COX-1 and COX-2 are the two types of COX enzymes. Prostaglandins related to COX-1 control homeostatic processes and are involved in the resolution of inflammation, but not the progression of inflammation [88]. Prostaglandins related to COX-2 are associated with inflammation from tissue injury [88]. Few studies investigate the specific mechanisms of WWB on COX enzymes. In one study [89], white willow bark inhibited COX-2-mediated PGE2 release in vitro. In an investigation of aspirin and salicylate, which have similar mechanisms to salicin, Higgs et al. [90] showed that both NSAIDS mediated PGE2. Furthermore, prostaglandin E2 has been commonly used as a measurement of inflammation in cattle [91,92]. Therefore, prostaglandin E2 will be measured in calves to understand the effects of WWB on inflammation.

3. Managing Transition Organic Dairy Heifer Behaviors and Udder Health

3.1. Challenges of Mastitis for Organic Dairy Farms

The National Organic Program of USDA sets the standards to which organic farmers have to adhere in order to produce organic products [2]. Organic dairy farming focuses on disease prevention and limits the use of synthetic drugs for the treatment of livestock diseases. For example, antibiotics are not allowed to treat animals unless the animals leave organic production immediately after. Unfortunately, some animals will still become sick despite best preventative practices.

In dairy cows, mastitis is one of the most common and economically important diseases [93]. Mastitis is an inflammation of the udder and will affect not only the animal's well-being, but also the milk's quality. In conventional production, mastitis is most commonly treated with intramammary antibiotics. However, this is not allowed for organic systems, and effective alternative treatment approaches are needed [32].

Udder health is important for the sustainability and optimal productivity of a dairy farm [94]). Milk from healthy cows, reflected by a low somatic cell count, has an improved shelf life and therefore receives a premium price. In addition, international trading partners such as Europe require on-farm bulk tanks with SCC under 400,000 and standard plate bacterial counts of less than 100,000 colony-forming units. Tikofsky et al. [95] reported that SCC for organic farms in New York averaged 273,000, whereas Zwald et al. [96] reported that 47% of organic farms in the upper Midwest had SCC greater than 300,000 and 15% had SCC greater than 400,000. Unfortunately, mastitis remains a common disease on dairy farms and is a leading cause for culling of cows [97]. The disease can reduce milk production and milk quality, impair animal welfare, and increase veterinary and labor costs. Effective treatment options beyond antibiotics are lacking [98]. Therefore, it is crucial for organic dairy producers to use effective strategies to prevent this disease and its associated losses. Recently, Hardie et al. [93] reported a mastitis incidence (13.8%) from organic Holsteins cows in the US and Ahlman et al. [97] reported that poor udder health is the main reason

for culling cows in organic herds. Recently, Fernandes [99] reported that elevated SCC in the first month of lactation had detrimental effects on the milk yield and survivability of dairy cows in USDA organic herds.

Organic dairy farms have reported some success and failures [30] with using alternative products for mastitis in cows. However, farmers have reported drying off the affected quarter, or—in severe cases—culling the animal as opposed to using alternatives to antimicrobials [100]. Mullen [101] evaluated the pharmacokinetics of garlic, thymol and carvacrol for use in controlling *S. uberis*-induced mastitis and reported that withhold times of at least 24 h should be established in organic herds that use these products. However, these products did not produce bacterial cures for mastitis [101]. Furthermore, researchers reported the efficacy of the herbal products (Phyto-Mast and Cinnatube) was similar to conventional therapies, and the products did not have any adverse effects on cows [102] Frequent stripping or the use of a topical udder rub are commonly used on organic farms [5]. The idea behind frequent stripping is that it removes the bacteria and bacterial toxin load from the udder to improve healing. Similarly, topical udder creams with peppermint or similar components are thought to decrease swelling and to improve blood flow and thereby improve the clearance of an infection from the udder. Although the rationale of both approaches is plausible, there are few data supporting the use of either therapy approach as effective treatment of clinical mastitis.

In dry-off, milk production is stopped, and in conventional and intensive dairy systems, therapeutic intervention is provided to cows to clear existing infections. However, intramammary antibiotics in dry-off are not allowed under the USDA National Organic Standards [2]. Some organic dairies may administer a variety of nonantimicrobial organic products [30,32], but clinical efficacy is lacking [33].

The dry period provides the udder with important time to regenerate and prepare for the next lactation. However, during the dry period, cows may be vulnerable to intramammary infections that may persist through the dry period and subsequently cause clinical mastitis early in lactation. Currently, in conventional and intensive systems, the dry-off procedure includes abrupt cessation of milking and applying blanket antibacterial treatment to prevent early dry period infections, but antibiotics are not allowed for organic herds. Current thought is to lower milk yield at dry-off to help prevent new infections during the early dry period [103], but reduction in feed has been associated with increased stress and metabolic disease incidence in dairy cows [104]. Intermittent milking at dry-off may reduce milk production with little to no discomfort to cows [104].

3.2. Challenges for Early-Lactation Heifers

First-calf heifers encounter several challenges following calving that can jeopardize animal welfare. Firstly, some heifers may become distressed when they encounter unfamiliar experiences related to being milked, such as unfamiliar sounds and smells in the milking parlor and tactile stimulation to the udder by handlers and milking units. Van Reenen et al. [105] reported that peak plasma cortisol concentrations were approximately 20% greater for heifers during milking on day 2 compared to day 130 of lactation, indicating that the beginning of the lactation period can be stressful. The typical lactation period is approximately 305 days, so 130 DIM represents mid-lactation. Sutherland and Huddart [31] also found similar results, in which heifers had 2.0 times the plasma cortisol concentration on the first DIM compared to the fifth DIM. Furthermore, authors also reported that plasma oxytocin concentrations after milking preparation procedures (but before milking unit attachment) were 2.4 times greater for heifers at 130 DIM compared to 2 DIM, indicating that heifers may need time to acclimate to milking [105]. Oxytocin is defined by the National Mastitis Council (https://www.nmconline.org/ (accessed on 9 November 2021)) as "the hormone produced in the pituitary gland that causes milk let-down".

Distressed heifers can endanger human handlers, because heifers may kick off milking clusters, kick at milkers or display undesirable behaviors that interfere with milking. This may increase injury to milkers and increase the risk of mastitis for the heifer [31,105].

However, many dairy farms already have voluntary milking systems and with these systems the risk of injury to the milkers is reduced or eliminated. Mastitis is defined by the National Mastitis Council (https://www.nmconline.org/ (accessed on 9 November 2021)) as "inflammation of the udder, most commonly caused by an infecting microorganism". For example, a prospective evaluation of all injuries by cattle at a hospital in New Zealand over a 1-year period conducted by Watts and Meisel [106] showed that hand or wrist injuries were commonplace and occurred after being kicked by a cow at milking time. In terms of udder health, Nitz et al. [107] found that heifers that detached milking cups during milking were 2.6 times more likely to develop new intramammary infections (IMI) between 3 and 17 DIM. In a study of 46 farms in Switzerland, Ivemeyer et al. [108] found that the number of kicks per cow displayed during milking was associated with new IMI infection incidences. Intramammary infection is defined as "the presence of an organism in the udder that is isolated from a milk sample". Therefore, aversive heifer behaviors during the early-lactation period may jeopardize both human and animal welfare.

In general, heifers are vulnerable to clinical mastitis and IMI during early lactation [108–111]. Clinical mastitis is defined by the National Mastitis Council (https://www.nmconline.org/ (accessed on 9 November 2021)) as "udder inflammation characterized by visible abnormalities in the udder or milk". In an observational study of 1014 heifers in Sweden, Persson Waller et al. [111] reported that 50% of the 364 recorded mastitis cases in heifers occurred within the first 6 DIM, and were primarily diagnosed as Staphylococcus aureus. This is a concern for farmers since poor udder health in heifers is associated with production, treatment, and labor costs. In 2009, Huijps et al. [112] estimated that the costs of clinical mastitis and IMI were $18.75 and $6.56 per heifer, respectively. In a more recent study in 2014, Cha et al. [113] estimated that the average cost of a clinical mastitis case ranged between $115 and $476 after considering mortality and reduced conception costs. Furthermore, poor udder health in early lactation may also put heifers at risk of future infections [114]. Poor milking behavior may increase the economic loss for farms due to increased risk of IMI [107], decreased milk productivity [115], and the risk of early culling [116]. The main reason for the culling of organic first-lactation cows was mastitis [97]. Furthermore, lower somatic cell score is associated with improved longevity of organic cows, because lower somatic cell score is associated with reduced incidences of mastitis [117]. Culling is the main management strategy for reducing mastitis in organic dairy herds, and heifers with mastitis during their first lactation were more likely to be culled than those heifers without mastitis. Rearing of organic dairy heifers is very costly because of high feed costs [99] and therefore, it is imperative to reduce mastitis in heifers.

3.3. Methods to Modulate Aversive Behaviors and Mastitis

Several approaches have been considered to reduce distress and prevent mastitis in heifers. In general, these strategies include handling heifers and familiarizing them with the milking parlor before calving [118,119]. For example, Hemsworth et al. [116] found that heifers that were accustomed to handling during calving had 40% fewer flinch, step, and kick responses during milking during the first 20 DIM compared to heifers that were not handled during calving. Bertenshaw et al. [120] reported that brushing heifers for 30 to 245 min during the last 6 weeks of gestation reduced kicking during milking up to the first 28 DIM compared to heifers that were not brushed. Das and Das [121] found that 30 udder massage sessions lasting 20 min each during the last 2 months of gestation improved temperament, milk letdown and milk flow rates over the first 16 DIM. Eicher et al. [118] reported that heifers that moved through the parlor (but were not milked) with lactating cows twice daily for 3 weeks prior to calving balked for a shorter amount of time while entering milking stalls on the first DIM compared to heifers prior to calving that did not receive any treatment. However, behaviors of shifting, stomping, kicking and kicking the milking unit off during milking were similar among treatments on the first DIM [118]. Kutzer et al. [119] reported that acclimation before calving, which consisted of familiarizing heifers to the milking herd 10 days prior to calving and moving them

through the milking parlor on at least 10 visits, reduced post-parturient stepping, kicking, ear-flattening, tail-tucking, and eye-widening behaviors in heifers over the first 7 DIM. However, intensive protocols to acclimate heifers to milking procedures may not be feasible for many farms due to labor challenges, so developing a protocol that fits within the capabilities of dairy farms is necessary.

A variety of strategies implemented during the pre-parturient period have been explored to prevent clinical mastitis and IMI, such as internal teat sealants [122], antibiotic therapies [123], milking [124], and repeated use of teat dip or spray [111]. However, some of these strategies, such as teat sealants and antibiotics, are not allowed in organic dairy animals in the US. In one experiment by Santos et al. [125], pre-parturient milking three times daily for 15 days prior to calving lowered the number of heifers with positive bacterial milk cultures by 25% on the first DIM and decreased the incidence of mastitis by 57% during the first 135 DIM. In another experiment, Lopez-Benavides et al. [126] reported that pre-parturient teat-spraying with an iodine-based disinfectant three times weekly for 21 days prior to calving reduced Streptococcus uberis in milk samples immediately after calving by 53% but did not reduce clinical mastitis. However, a reduced labor force may prevent the adoption of these strategies on many farms. Therefore, current pre-parturient strategies for preventing clinical mastitis and IMI in heifers must be improved to be practicable on farms in terms of labor limitations.

Aversive behaviors are behaviors that are undesirable to human handlers. These include behaviors that endanger handler safety and behaviors that interfere with milking efficiency. Commonly examined aversive milking behaviors include stomping, kicking, and kicking the milking unit off. Ease of milking parlor entry is also important, as aversive behaviors such as balking may interfere with milking efficacy [118]. Furthermore, objective temperament scores are commonly used to describe the overall reactivity of cows to stressors related to milking [121]. Aversive behaviors may also be indicative of distress in heifers. Temperament scores and measurements used in current assessments include milking speed, milk flow rate, approach test, novel test, handling temperament, heart rate, general temperament, and automated milking system temperament [127]. Hemsworth et al. [116] found that milk cortisol concentrations were associated with flinch, step, and kick responses in heifers, indicating that these behaviors may be indicative of distress. Fogsgaard et al. [128] reported cows with mastitis were more restless during milking, indicated by greater frequencies of tripping and kicking, suggesting that the presence of these behaviors may indicate pain caused by mastitis.

Furthermore, Phillips et al. [129] found that first-lactation cows that had their teats cleaned and were teat-dipped weekly 3 weeks prior to calving had reduced kicking and restlessness behaviors during post-calving milking. Cows had lower IMI caused by Staphylococcus aureus post-calving. Adjusting heifers to the milking parlor prior to calving may improve first-lactation cow well-being and promote a positive human–animal relationship.

4. Conclusions

Organic dairy production is a worthwhile method of dairy farming with steady and emerging markets. However, many farmers are apprehensive of organic dairy production practices because of concerns that no antibiotic use may have a negative impact on herd health. Alternative therapies to improve animal welfare must be researched in organic livestock production to verify that their use improves animal well-being. Critics of organic dairy management practices are concerned that producers use ineffective approaches to care for animals. However, the successful management of organic dairy herds depends on disease prevention through the use of traditional good husbandry practices.

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Appendix 4

Animal Care

Reference Manual Version 4
2020-2022

This manual is not a legal document and is intended for educational purposes only. Dairy farmers are individually responsible for determining and complying with all requirements of local, state and federal laws and regulations regarding animal care.

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01

Introduction

About FARM

Today's consumers expect and deserve safe, wholesome dairy products from people who are producing it responsibly.

U.S. dairy farmers have a strong track record of providing excellent animal care. The National Dairy Farmers Assuring Responsible Management (FARM) Program demonstrates dairy farmers' ongoing commitment to the highest standards in the industry. The FARM Program also demonstrates that **farmers are doing what's right for cows, customers and consumers** — consumers who are more curious and skeptical than ever before about how food is raised and produced.

As science and best practices evolve alongside public attitudes and perceptions, the dairy industry must continue to show customers and consumers that we're holding ourselves to the highest standards of animal care. The FARM Program does just that.

Launched in 2009, the FARM Program helps earn the public's trust, demonstrating that dairy farmers share their values and are committed not only to quality animal care, but also to ensuring safe, wholesome milk, high standards of environmental stewardship and exceptional work environments through its four program areas. The Animal Care Program is the cornerstone of the FARM Program. More than 98% of the U.S. milk supply comes from participating farms.

FARM Program Areas

ANIMAL CARE

ENVIRONMENTAL STEWARDSHIP

ANTIBIOTIC STEWARDSHIP

WORKFORCE DEVELOPMENT

FARM works with you, the producer community and industry partners, to provide comprehensive resources, ongoing training and other educational tools. These tools help create a culture of continuous animal care improvement.

The goal of FARM is to unite the dairy industry around best management practices and demonstrate the excellence that occurs on your farm every day through science and outcome-based standards that are facility, size and geography neutral. The on-farm evaluation serves as a snapshot in time of those best management practices. However, The FARM Program can only provide the foundation and framework of excellent animal care. Farmers must take forward and instill daily excellence in animal care through their farms' culture by way of active leadership, oversight and management. FARM does not ensure a culture, guarantee best management practices are followed, or replace supervision or management.

Animal Care Standards

SCIENCE Based

OUTCOMES Based

Implementing FARM

Created by the National Milk Producers Federation (NMPF), with support from Dairy Management, Inc. (DMI), the FARM Program raises the bar for the entire dairy industry — creating a culture of continuous improvement.

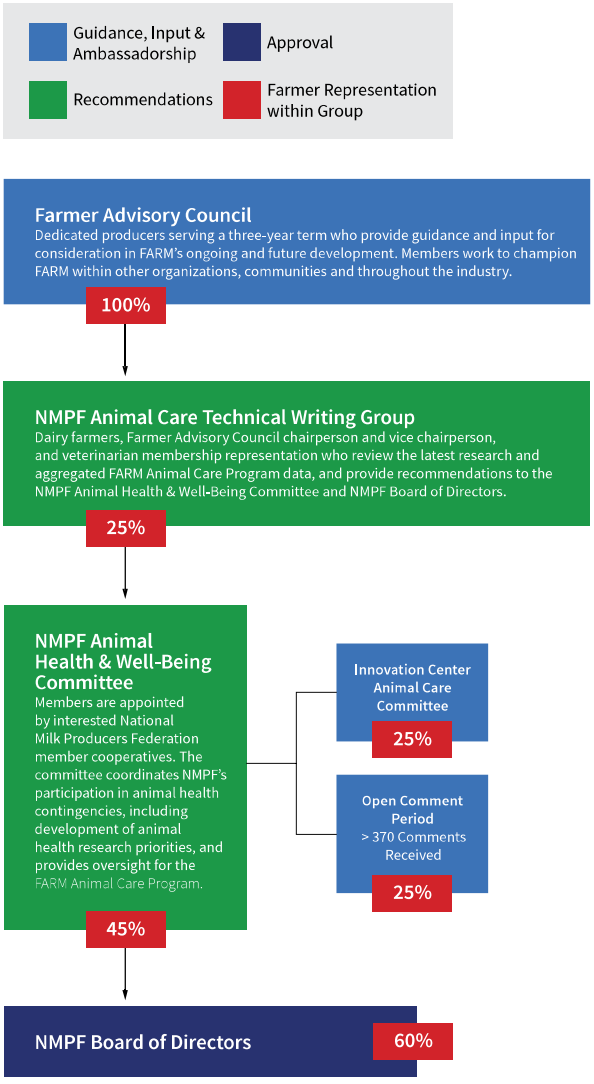
The FARM Animal Care Program establishes:

- On-farm best management practices
- Standards for on-farm second-party evaluations
- Third-party verification to guarantee the rigor and integrity of FARM Animal Care Program implementation

The FARM Program provides comprehensive resources to implement the program at the farm and participant level, including manuals, templates, posters and videos available online at nationaldairyfarm.com.

Program Governance

The FARM Animal Care Task Force, which includes representation from dairy farmers, the veterinary community, co-ops, processors, dairy organizations and university animal care experts, guides the program — ensuring that it fosters a culture of continuous improvement and that the best management practices, which are the cornerstone of the program, evolve with the latest animal care research.



Participants

The FARM Animal Care Program participants include any cooperative, proprietary processor, milk handler or organization that has a signed current FARM participation agreement on behalf of their membership, patrons or direct shippers. Participants manage the FARM Animal Care Program on behalf of the farms and facilities belonging to the milk handling entity.

Second-Party Evaluation

The second-party evaluation, completed on every participating dairy facility at least once every three years, provides dairy farms with an external review of their animal care practices based on FARM Program guidelines.

The results of the second-party evaluation provide dairy farmers with a snapshot overview of the farm's current animal care practices. If the second-party evaluation identifies areas of improvement, action plans are generated to demonstrate continuous improvement toward the industry's best animal care practices and standards.

Only qualified individuals who have completed the annual FARM certification training are qualified to conduct evaluations. Typically, second-party evaluators are co-op/processor staff, veterinarians or independent dairy consultants.

Evaluators must have a minimum combination of five years of education – including animal science, dairy science or other relevant curriculum – and/or on-farm (dairy) experience. Evaluators must apply, complete a phone interview, attend classroom and on-farm training, pass competency exams and recertify annually.

Second-Party Evaluators

Trained second-party evaluators work with you to identify strengths and, if necessary, outline improvements. They work alongside dairy farmers to ensure the highest standards of animal care.

Facility Certification

A dairy facility is considered certified in the FARM Animal Care Program if it:

- Is up to date with the FARM Animal Care Program evaluation, in accordance with the program's evaluation cycle
- Does not have any overdue corrective action plans
- Is not subject to the FARM Willful Mistreatment or Neglect Protocol

Accountability Measures

At the conclusion of a second-party evaluation, if FARM Animal Care Program standards are not met, corrective actions may be generated. Corrective action accountability measures are categorized by level of significance:

- Immediate Action Plan (IAP)
- Mandatory Corrective Action Plan (MCAP)
- Continuous Improvement Plan (CIP)

Corrective actions can lead to conditional certification and conditional decertification if left unresolved beyond the timeframes designated by FARM, or sooner per the program participant.

Immediate Action Plan (IAP)

An IAP is triggered if a facility fails to comply with the FARM Program standard that bans routine tail docking. Failure to meet the standard will result in the facility being placed on conditional certification for resolution within 48 hours. If the facility meets the standard by resolving this action plan within 48 hours, a follow-up will be conducted by an second-party evaluator at one week, one month and three months to ensure routine tail docking has ceased.

If the facility continues to not meet the standard after this timeframe, the facility will be conditionally decertified until the standard is met.

Mandatory Corrective Action Plan (MCAP)

Additional best management practices have been identified as having significant importance in ensuring sound animal care. The following FARM Animal Care standards, if unmet at the time of an evaluation, will generate a MCAP.

MCAP

FARM Program standards require that MCAPs are met within nine months. However, a participant/evaluator may require that a standard be met before the nine-month deadline.

Failure to meet these standards within the allotted timeframe will result in the facility being placed on conditional certification, leading to conditional decertification if standards are not met in a 60-day period.

Veterinarian Review

- The facility has a written Veterinarian-Client-Patient Relationship (VCPR) form that is signed by the farm owner and Veterinarian of Record (VOR) annually.
- The written herd health plan is reviewed annually by the VOR.

Pre-Weaned Calves

- Pre-weaned calf protocols and practices must demonstrate that pre-weaned calves are:
  - Disbudded prior to 8 weeks of age
  - Moved using proper methods
  - Provided feed and water access by day 3
  - Provided quality and quantity colostrum/colostrum replacer and milk/milk replacer

Non-Ambulatory Animals

- Non-ambulatory animal protocols and practices must demonstrate non-ambulatory animals are:
  - Moved using proper methods
  - Provided prompt medical care
  - Provided access to feed, water, protection from heat and cold for typical climatic conditions, isolation from other ambulatory animals and protection from predators

Euthanasia

- Euthanasia protocols and practices demonstrate the following:
  - Criteria for the identification of animals to be euthanized are established
  - Euthanasia techniques follow the approved methods of American Association of Bovine Practitioners (AABP) and/or American Veterinary Medical Association (AVMA)
  - Carcass disposal is conducted using the appropriate method

Fitness to Transport

- Acceptable fitness to transport protocol

Water and Feed Access

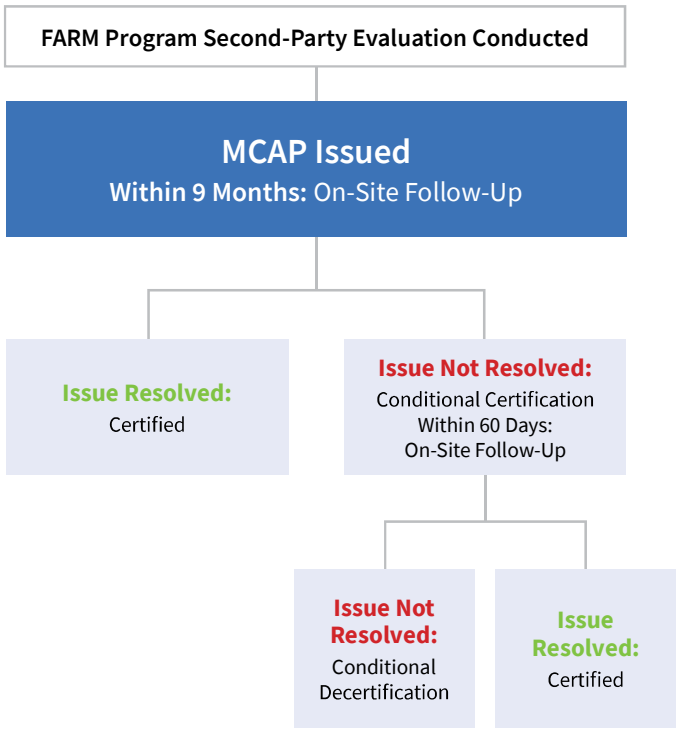
- Feed access for all age classes; pre-weaned calves by day 3
- Water access for all age classes; pre-weaned calves by day 3

Continuing Education

- Signed Cow Care Agreement for any **non-family employees** with animal care responsibilities
- Job-specific continuing education for **non-family employees** with animal care responsibilities, if they are responsible for:
  - Stockmanship/handling
  - Pre-weaned calf care
  - Non-ambulatory animals
  - Euthanasia
  - Determining animals that are fit for transport

The MCAP will be created with their second-party evaluator with a set timeframe for re-evaluation of progress toward completing all MCAPs, not to exceed nine months.

FIGURE 1: Mandatory Corrective Action Plan Overview



Continuous Improvement Plans (CIP)

Animal observation benchmarks and additional best management practices have been identified as areas that also demonstrate excellence in animal care.

The following FARM Animal Care standards, if unmet at the time of an evaluation, will generate a CIP.

CIP

FARM Program standards require that CIPs are met within three years or less, however, a participant/evaluator may require that a standard be met before the three-year deadline.

Failure to meet the standard within this allotted timeframe will result in the facility being placed on conditional certification, leading to conditional decertification if standards are not met in a 60-day time period.

Evaluators and participants can create CIPs for additional standards that have not been designated by FARM.

Animal Observation Benchmarks

- **Body condition score** | 99% or more of all animals 3 days of age and older have a body condition score of 2 or greater on the FARM body condition scorecard
- **Hock/Knee** | 95% or more of the lactating herd score 2 or less on the FARM hock/knee scorecard
- **Locomotion** | 95% or more of the lactating herd score 2 or less on the FARM locomotion scorecard
- **Broken tails** | 95% or more of lactating animals do not have broken tails

Pain Management

- Acceptable pain management protocols and practices for disbudding

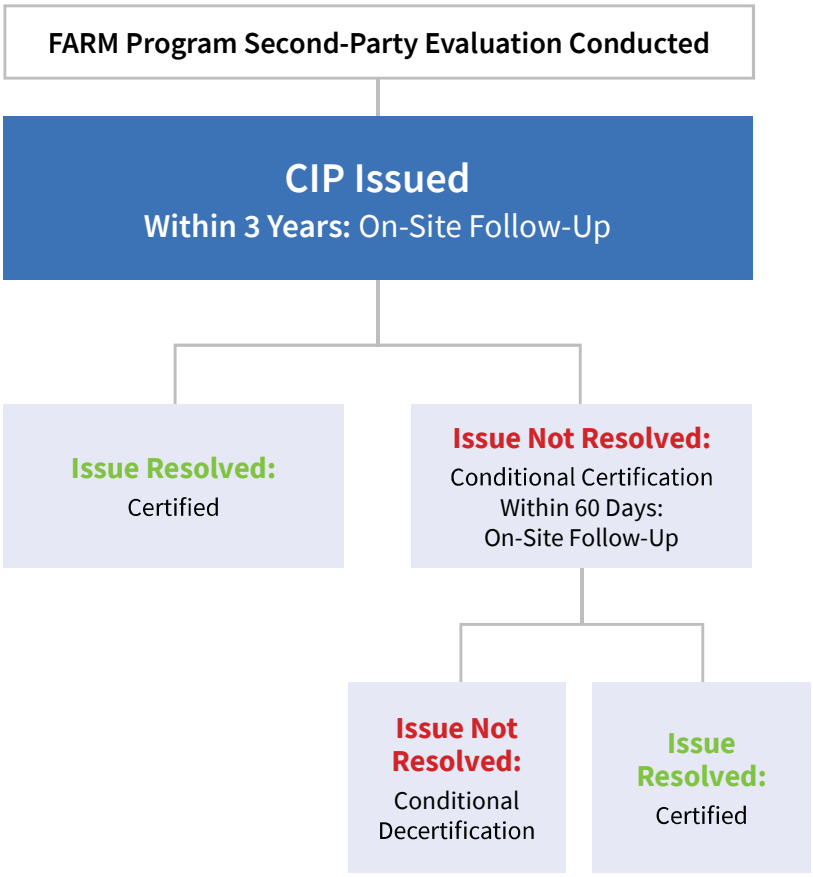
Treatment Records

- Maintain permanent written or electronic drug treatment records

Continuing Education

- Signed cow care agreement for any **family employees** with animal care responsibilities
- Job-specific continuing education for **family employees** with animal care responsibilities, if they are responsible for:
  - Stockmanship/handling
  - Pre-weaned calf care
  - Non-ambulatory animals
  - Euthanasia
  - Determining animals that are fit for transport

FIGURE 2: Continuous Improvement Plan Overview



Conditional **Certification**

If corrective action plans are not satisfactorily resolved by the date set by FARM or the FARM Animal Care participant, the facility will have a conditional certification for up to 60 days. A FARM Animal Care participant may continue to market milk from a facility with a conditional certification and remain in good standing with FARM. If the plan is resolved within the 60-day period, the facility will be returned to full certification status.

Conditional **Decertification**

If corrective action plans are not satisfactorily resolved by the date set by FARM or the FARM Animal Care participant, and the facility has had conditional certification for 60 days without satisfactorily resolving the plan, the facility will be considered conditionally decertified. A FARM Animal Care participant may not continue to market milk from a facility with a conditional decertification and remain in good standing with FARM. Evidence of plan resolution must be provided to FARM for the facility to be returned to full certification status.

Third-Party Verification

Once a second-party evaluation is complete, the dairy facility is eligible to be randomly selected, through statistical sampling, to undergo third-party verification. Statistical sampling includes selection criteria like FARM participant geographic location, size and operation type to ensure that the number of randomly selected dairy farms mirrors participants in the entire program.

Verification helps ensure the program accomplishes its goals and objectives by confirming the second-party evaluators are upholding the integrity of program implementation. Third-party verifiers must meet the same qualifications as second-party evaluators.

FARM Integrity

Qualified third-party verifiers evaluate a representative percentage of farms each year to ensure program integrity.

USING THE MANUAL

This Animal Care Reference Manual is an easy-to-use, comprehensive resource detailing animal care and management guidelines of the FARM Program. It's an educational tool for all participating dairy farmers, co-ops, proprietary processors, trained second-party evaluators and third-party verifiers.

Along with the guidelines, this document provides extensive information, resources and references that while thorough, are not exhaustive nor prescriptive for singular approaches toward meeting the guidelines of the program. This reference manual is not a legal or regulatory requirement for the dairy industry. It is intended to serve as a wide-ranging educational resource for the U.S. dairy industry.

Best practices identified in the manual are not the only practices that can meet the identified guidelines. Application of management practices may vary due to regional norms, weather or other conditions. Dairy farmers should work with their trusted advisors and management team members to develop appropriate management approaches to meet the identified guidelines.

FARM Program materials are living documents. Guidelines are reviewed every three years by the FARM governance committees and are subject to updates based on new, science-based animal care and well-being research. This is part of the FARM Program's commitment to continuous improvement.

Management Checklists

The management checklist details key on-farm guidelines and best practices. Management checklist points are listed at the beginning of each chapter and within the chapters under corresponding topics.

Here is one example of a management checklist point:

✓ **The facility has a written Veterinarian-Client-Patient Relationship (VCPR) that is signed by the farm owner and Veterinarian of Record (VOR) annually.**

Appendix 4

02

Veterinarian Review

Appendix 4

Management Checklist

✓ **The facility has a written Veterinarian-Client-Patient Relationship (VCPR) that is signed by the farm owner and Veterinarian of Record annually within 12 months.**

✓ **The written herd health plan is reviewed annually by the Veterinarian of Record.**

✓ **The facility has permanent (written or electronic) treatment records for the treatment of the facility's common diseases.**

Records include:

- *Date of treatment*
- *Animal treated identification*
- *Name of treatment used*
- *Disease/condition being treated*
- *Dosage administered*
- *Route of administration*
- *Duration of the treatment*
- *Specified withdrawal times for milk and meat to ensure food safety*

Expectations of the Veterinarian Community

Dairy veterinarians serve as trusted partners to farmers across the country. As continued research and innovation drive change in on-farm animal care, the veterinarian's role is more important than ever before. It's not just about treating sick animals. It's about working hand in hand with farmers to provide guidance when it comes to cow comfort, disease prevention, antimicrobial stewardship, herd health and overall animal care.

Dairy veterinarians must strive to be engaged, open-minded and forward-thinking team members who maintain open lines of communication with their clients. It's vital for veterinarians to stay up to date on the latest research-based practices and protocols for dairy animal welfare and judicious antibiotic use, and dedicate themselves to thorough on-farm observation of routine procedures to ensure the latest guidelines are in place and being followed.

Veterinarian-Client-Patient Relationship (VCPR)

✓ **The facility has a written Veterinarian-Client-Patient Relationship that is signed by the farm owner and Veterinarian of Record annually within the previous 12 months.**

The dairy farmer and farm veterinarian should have a robust relationship to ensure animal care.

The VCPR is one of the cornerstones of the FARM Animal Care Program and, as such, veterinarians must sign a VCPR annually to document their involvement and formalize the relationship. VCPR guidelines provide expectations of responsibility related to animal care for the farmer and veterinarian.

Farm visits and treatment record evaluation are an important component of a valid VCPR. Veterinarians should proactively work alongside farmers to develop herd health plans for all age groups of animals to prevent illness and injury.

There are many facets to a comprehensive VCPR. The AABP identifies the following areas that are critical components for establishing and maintaining a VCPR:

Maintain Written Agreements for Working Relationships

- A veterinary practice or individual should establish a written agreement with the client that identifies the farm veterinarian who is accountable for drug use and treatments administered to the cattle on the farm.
- If more than one veterinarian or veterinary practice has a working relationship on the operation, then the agreement should identify which one has the overall responsibility for treatment protocols, drug inventories, prescriptions, personnel training, oversight and drug use on the operation.
- The identified veterinarian is referred to as the VOR.

Have a Veterinarian of Record (VOR)

- The VOR is the responsible party for providing appropriate oversight of drug use on the farm operation. Such oversight is a critical component of establishing, maintaining and validating a VCPR.
- This oversight should include, but may not be limited to, establishing treatment protocols, personnel training, treatment records review, drug inventory monitoring and assuring appropriate labeling of drugs. Veterinary oversight of drug use should include all drugs used on the farm regardless of the distribution of the drugs to the farm.
- Regular farm visits are an essential component to providing such oversight, however this can be supplemented through laboratory data evaluation, records evaluation and communication via phone, email, text or other routine communication forms. The frequency of farm visits should be determined by the VOR based on the type and size of the operation.

Clarify Any and All Relationships With Consultants and Other Veterinarians

- If a veterinarian who is not the VOR provides professional services in any type of consultative or advisory capacity, then it is incumbent on that veterinarian to ensure that the VOR is contacted and informed of their findings and recommendations.
- No protocols or procedures that have been established by the VOR should be changed unless or until there is an agreement by all parties about such changes. The agreement between the VOR and the client should establish which management groups of the farm operation are covered in the agreement. For instance, reproduction, milk quality, youngstock/replacement, feedlot, cow-calf and sick animal treatments are possible identifiable areas.

Provide Written Protocols

- Protocols and treatment guidelines for commonly occurring, easily recognizable conditions should be established in writing and agreed upon by all parties involved. They should be signed and dated.
- Training of personnel authorized to use drugs on the operation should be undertaken and periodically reviewed. The frequency of such training and review should be determined by the size and type of the operation, the rate of personnel turnover, and the changes in protocols and procedures.
- Treatment protocols and procedures should include all drugs used on the operation (over-the-counter, prescription, extra-label, veterinary feed directive (VFD) and water soluble). All protocols should clearly define when to quit treating and seek professional help (poor response, increase in severity of signs, etc.).

Ensure Written or Electronic Treatment Records Are Maintained

- Written/electronic treatment records of all animals or groups of animals treated are an essential component of maintaining and establishing the VCPR and decreasing the risk of violative drug residues. Such records should include, at a minimum:
  - Date of treatment
  - Animal treated identification
  - Name of treatment used
  - Disease/condition being treated
  - Dosage administered
  - Route of administration
  - Duration of the treatment
  - Specified withdrawal times for milk and meat to ensure food safety

Periodic and timely review of the treatment records, drug inventories and usage is an important part of oversight by the VOR.

Provide Drugs or Prescriptions for Specific Timeframes and for Specific Protocols

- Provision of drugs or drug prescriptions should be for specific timeframes appropriate to the scope and type of operation involved and only for the management groups within the operation over which the VOR has direct involvement and oversight. Additionally, failure to follow agreed upon protocols and procedures should be grounds for denial of provision of drugs or prescriptions except for an individual patient needing treatment at the time of examination.
- Routine examination of drug inventories on farm and product purchase records review (pricing information is unnecessary) are recommended. Cooperation with distributors is encouraged.
- Establishment of a VCPR for the sole purpose of drug sales or increased sales of a brand of drug is not a valid or ethical reason for having a VCPR.

Dairy farmers are encouraged to review treatment protocols and antibiotic stewardship principles or programs, including the AABP "Guidelines for Establishing and Maintaining the VCPR in Bovine Practice," the FARM Program Milk and Dairy Beef Drug Residue Prevention Manual and Food Armor. Dairy farmers should consult their veterinarian.

A veterinarian may develop an area of animal health management expertise and may serve as the primary veterinarian for one specific part of a dairy farm. For example, there may be one primary veterinarian for reproduction protocols and another primary veterinarian for metabolic issues. Dairy farmers should ensure that any veterinarian providing prescription medication or protocols for use on a farm notify the designated VOR for that farm.

Food Armor offers an online learning platform to advance skills and knowledge around antimicrobial stewardship practices. Through a self-paced program, Food Armor comprehensively guides learners through developing the habits and tools to empower themselves and their on-farm teams. These courses are designed specifically for the veterinarian and farmer audiences and offer a practical framework for implementing antimicrobial stewardship plans on farms.

✓ **The written herd health plan is reviewed annually by the Veterinarian of Record.**

Written protocols and procedures should provide enough detail to ensure that all family and non-family employees with animal care responsibilities can routinely and consistently perform their animal care duties. As a best practice, written protocols are reviewed at least annually and updated as necessary with the VOR.

A comprehensive herd health plan that meets all outlined FARM Animal Care Program standards should include written protocols for the following management areas:

- **Pre-weaned calf management**
- **Non-ambulatory animal management**
- **Euthanasia**
- **Fitness to transport**
- Treatment of common diseases
  - Mastitis
  - Metritis
  - Milk fever
  - Ketosis
  - Displaced abomasum
  - Pneumonia
  - Diarrhea
- Vaccinations
- Milking procedures
- Lameness prevention and treatment
- Difficult calvings
- Biosecurity
- Fly control
- Parasite control
- Pest control
- Branding (if conducted)
- Castration (if conducted)

These animal care standards, if unmet at the time of an evaluation, will generate a MCAP.

Fillable written protocol templates are available from the FARM Program and Food Armor. Other protocols that meet the same content requirements as the templates are acceptable.

✓ **The facility has permanent (written or electronic) treatment records for the treatment of the facility's common diseases that include:**

- Date of treatment
- Animal treated identification
- Name of treatment used
- Disease/condition being treated
- Dosage administered
- Route of administration
- Duration of the treatment
- Specified withdrawal times for milk and meat to ensure food safety

Keeping adequate drug treatment records for food-producing animals may seem menial, but good control measures can help keep unsafe food from reaching consumers.

Keeping drug records can:

- Prevent an accidental violative residue
- Ensure an effective herd health plan
- Improve a veterinarian's effectiveness
- Reduce liability (drug records are required by law)
- Save money

Veterinarians must maintain written or electronic records for all animals treated for at least 2 years (or as otherwise mandated by federal or state law), to document that the drugs were supplied to clients in line with federal and state rules and policies. Record keeping allows for the veterinarian to have a history to which he/she can refer to prescribe effective therapy and to serve as protection in case of regulatory follow-up.[1]

Farmers should also keep written or electronic records on all animals treated with drugs for at least 2 years per the Food and Drug Administration regulatory requirements. The records system should be easily accessible to everyone who works with the animals.

EXAMPLE RESOURCES

Veterinarian-Client-Patient Relationship Validation Form

Drug Treatment Record Veterinarian Review Form

Individual Animal Treatment Record

Daily Treatment Record

Recommended or Approved Drug List

Visit **nationaldairyfarm.com** for record keeping, drug management record forms and other free resources

Appendix 4

03

Continuing Education

Management Checklist

- ✓ All family and non-family employees with animal care responsibilities must sign a cow care agreement annually.
- ✓ All family and non-family employees with animal care responsibilities are trained annually in proper stockmanship.
- ✓ Family and non-family employees with pre-weaned calf management responsibilities have been trained annually on the written protocol for pre-weaned calf management.
- ✓ Family and non-family employees with non-ambulatory animal management responsibilities have been trained annually on the written protocol for non-ambulatory animal management.
- ✓ Family and non-family employees with euthanasia responsibilities have been trained annually on written protocol for euthanasia.
- ✓ Family and non-family employees with determining fitness to transport responsibilities have been trained annual on written protocol for fitness to transport.

National Dairy FARM Animal Care continuing education standards are valid for all family and non-family labor (over age 18) with animal care responsibilities in the respective areas.

All non-family labor must have individualized documentation.

All family and non-family employees with animal care responsibilities must sign a cow care agreement annually.

Humane handling and animal care should be part of the daily culture on the dairy – not just an annual training. Reinforce humane animal handling and animal care expectations throughout job expectations and daily functions. Animal abuse is never tolerated.

Continuing education and training give farm workers the opportunity to increase their knowledge and skill, which in turn makes them more valuable to the farm. No matter the size of the dairy, providing continuing education and training for family and non-family employees with animal care responsibilities ensures not only that the basics of low-stress animal handling and a zero-tolerance for abuse are understood, but also clearly conveys job expectations and establishes the dairy's culture.

Continuing education and training should encompass care expectations for particular circumstances, like how to move cattle or what to do in case of emergency, as well as general expectations, like how to implement a specific protocol.

"Family" Defined

An immediate family member is defined as grandparent, parent, in-law, spouse, partner, sibling, child or grandchild of the legal owner(s) of the dairy operation.

When farm workers are given opportunities to broaden their knowledge and increase their skill level, they are more engaged and productive. Training and continuing education also allow a farm to hire entry-level workers and train them for the jobs for which they are needed, rather than trying to find workers that already have the needed skills and experience, which can be a challenge in communities with a limited labor pool.

Ultimately, training and developing workers is good for business and helps dairies remain competitive while dealing with a shortage of skilled, qualified workers.

Family Employees Continuing Education Criteria

On facilities with family employees, one family member can be accountable for and sign one cow care agreement on behalf of all family employees. Similarly, one family member can document and sign to confirm that other immediate family members (18 years and older) have been trained or provided continuing education in each required area.

Family and non-family employees with animal care responsibilities have been trained annually in proper stockmanship

- ✓ **Family and non-family employees with pre-weaned calf management responsibilities have been trained annually on pre-weaned calf management written protocols. (See Chapter 7)**
- ✓ **Family and non-family employees with non-ambulatory animal management responsibilities have been trained annually on non-ambulatory animal management written protocols. (See Chapter 8)**
- ✓ **Family and non-family employees with euthanasia responsibilities have been trained annually on euthanasia written protocol. (See Chapter 9)**
- ✓ **Family and non-family employees who are responsible for determining fitness to transport have been trained annually on fitness to transport written protocol. (See Chapter 10)**

Stockmanship

There are two primary concerns when handling dairy animals: animal comfort and safety, and animal caretaker safety. Animal caretakers should be trained or provided continuing education opportunities to learn proper handling techniques and appropriate use of restraint equipment. **Abuse is never tolerated.**

Animals should be handled by equipment appropriate for the procedure. Use of flags, plastic paddles and a stick with ribbon attached to it are appropriate for expanding the handler's presence but should not come in direct contact with the animal. **Management must be attentive to and correct excessive or routine aggressive contact, slapping or prodding.** In all cases, use the least amount of force necessary to control the animal while ensuring the safety of herdmates and animal caretakers.

All cattle restraint equipment and housing areas should have provisions for the humane release and removal of non-ambulatory or distressed cattle. Preferably, use equipment with emergency release devices.[1]

For cattle, routine contact and gentle handling by humans beginning at birth will reduce fear and flight distance, make observation and treatment easier, improve productivity and enhance animal care. Cattle should be moved at a slow walk. Control the herd's speed in lanes and alleyways to prevent crowding at corners, gates and other narrow places in a facility.[2]

Never use a tail aggressively to move a cow. Tails can be broken through twisting, jacking or other rough handling. An observation of aggressive tail use can detect farm-wide problems in animal handling. A widespread presence of broken tails indicates that there is, or has been, a problem on the farm. Investigate patterns in tail breaks considering the age class affected, the location of the breaks within the tail, and by observing handling to determine when and how tails are being broken.

Noise

Loud noises are known to be unpleasant for cattle, so make every effort to minimize loud noises during routine management practices such as handling, milking and transport. In best practice, take care to minimize all noises, including noises from equipment and personnel. Dairy cows do not respond positively to excessive noise or yelling. Animal handlers should minimize noisy behavior and treat animals — and other employees — with respect.

Types of Continuing Education

Continuing education can be offered through a variety of methods. The following is a non-exhaustive list of opportunities and programs that can be used for annual continuing education and training:

- Discussions with or presentations from on-farm dairy industry stakeholder specialists
  - *Veterinarians*
  - *Nutritionists*
  - *Technical service teams (pharmaceutical, reproduction, milk quality, etc.)*
  - *University and extension faculty and staff*
  - *Beef Quality Assurance state coordinators*
- Attendance of dairy industry meetings
- Formal dairy employee training programs
- Job shadowing with management
  - *Example: A newly hired milker job shadows a milking shift supervisor for a period of time. Management confirms with the milking shift supervisor that the new employee is appropriately trained and can begin milking independently.*
- Formal education
  - *Examples:*
    - Animal husbandry classes at universities
    - Continuing education class offerings by dairy industry-led program (i.e., U.S. Dairy Education and Training Consortium, Penn State Online Dairy Production and Management, etc.)
- Print and digital media training
  - *Examples:*
    - Employees, over lunch break, watch the FARM stockmanship training video in 5-10 minute segments throughout the month.
    - Sharing relevant news articles in Dairy Herd Management on proper calf feeding techniques and nutritional requirements with a new weekend calf feeder.

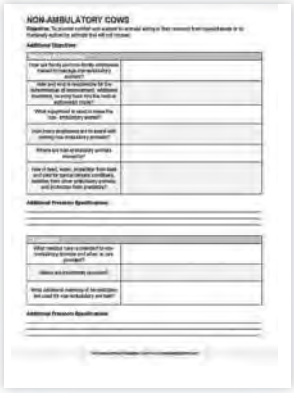
A list of training aids and resources can be found on the National Dairy FARM Program website at nationaldairyfarm.com.

EXAMPLE RESOURCES

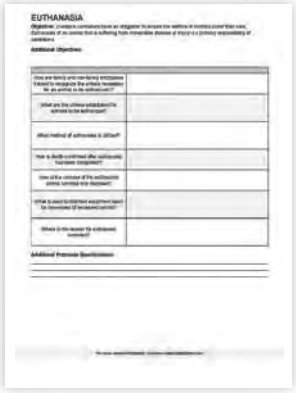
Cow Care Agreement

Stockmanship Training — Video and Quiz

Pre-Weaned Calf Protocol



Non-ambulatory Cow Protocol



Euthanasia Protocol

Fitness to Transport Protocol

Visit **nationaldairyfarm.com** for more resources,
and free continuing education and protocol templates

FARM encourages dairy producers to implement the **See it? Stop it! program.**

See it? Stop it! is a national initiative that confirms the culture of care that farm owners and managers demand of every person who comes in contact with their animals. The purpose is to:

- Highlight the integrity of the farm's philosophies on responsible animal care
- Help staff understand their important role in animal protection
- Provide clear direction to employees who suspect or witness deliberate animal abuse, neglect, harm or mishandling on how to immediately report it to a supervisor or other individual responsible for enforcement of proper animal care

Materials, both in English and Spanish, include a program overview, initiative values, poster, brochure, PowerPoint presentation and employee agreement and checklist. See it? Stop it! helps producers confirm their obligation to great animal care and their commitment to ensure those in contact with their animals do the same.

04

Facility Management

Management Checklist

Feed and Water

- ✓ All age classes of animals have access to clean water appropriate for climatic conditions.
- ✓ All age classes of animals have access to sufficient quantities of feed for maintenance, health and growth.

Protection from Heat and Cold

- ✓ All age classes of animals are protected from heat and cold for typical climatic conditions.

Housing

- ✓ All age classes of animals have housing that allows for the ability to easily stand up, lie down, adopt normal resting postures and have visual contact with other cattle without risk of injury.
- ✓ All age classes of animals have a resting area that is clean, dry, provides traction at all times when away from the milking facility and does not pose risk of injury.
- ✓ All age classes of animals have a method of daily exercise (weather permitting, if outdoors).

Facility Design

- ✓ Facilities are designed to prevent injuries, slips and falls of animals.
- ✓ Facilities are designed to prevent unnecessary contact with electrical currents.
- ✓ Facilities are designed to have adequate lighting for animal observation and family and non-family employees with animal care responsibilities safety.
- ✓ Facilities are designed to provide proper ventilation in all housing facilities that reduces odors, dust and/or noxious gas.

Emergency Preparedness

- ✓ The facility has names, telephone numbers and the site address posted in a prominent location, in the languages understood by family and non-family employees with animal care responsibilities, for emergency preparedness.
- ✓ The facility has a written emergency action/crisis plan to effectively manage emergencies or crises that may occur.

Proper management of cattle housing environments has been linked to improved animal performance and overall well-being. Facilities include all housing structures, handling structures, lots, pens, stalls, alleys and pastures that are inhabited by cattle of any age.

Feed and Water

- ✓ **All age classes of animals have access to clean water appropriate for climatic conditions.**
- ✓ **All age classes of animals have access to sufficient quantities of feed for maintenance, health and growth.**

Nutritional management is key to excellent animal health. All animals should have consistent, daily access to adequate feed and water, according to their specific requirements. Rations should provide the required nutrients for maintenance, growth, stage of lactation, health and pregnancy based on an animal's life stage. Body condition scoring is a valuable outcomes-based measure that can be used to monitor the nutritional condition of the herd.

Water

Fresh, clean water is essential for animal health and well-being. Access to waterers — large tanks, troughs, buckets or fountains — is essential for cattle to satisfy their need for water. Waterers should be easily accessible for the animals to reach on demand and should accommodate the number of animals in the group (number, size and capacity).

Continuous access to water is best practice. When continuous access is not possible (i.e., in freezing climatic conditions), make water available at least twice per day and allow animals to drink to satiation. **See TABLE 1** for the estimated water consumption requirements of dairy cattle.

Additional considerations for water include:

- Locate waterers near feed troughs and stalls
- Monitor and maintain water cleanliness through routine cleaning
- Provide access to water in return alleys from the milking parlor to promote consumption immediately after milking

Feed

TABLE 1: Estimated Water Consumption of Dairy Cattle

ESTIMATED DAILY WATER CONSUMPTION FOR A 1,500-POUND LACTATING COW PRODUCING 40 TO 100 POUNDS OF MILK DAILY.[a]

Milk Production (lbs/day)	Estimated DM Intake (lbs/day)	Mean Minimum Temperature[b] GALLONS PER DAY[c]				
		40°F	50°F	60°F	70°F	80°F
40	42	18.4	20.2	22.0	23.7	25.5
60	48	21.8	23.5	25.3	27.1	28.9
80	54	25.1	26.9	28.7	30.4	32.2
100	60	28.5	30.3	32.1	33.8	35.6

[a]Sodium intake = 0.18% of DM intake • [b]Mean minimum temperature typically is 10 to 15°F lower than the mean daytime temperature • [c]1 gallon of water weighs 8.32 pounds.

As a best practice for animal health, routinely monitor feed quality and nutrient content of feed components.

By working with a dairy nutritionist, a dairy operation can evaluate its feeding program to ensure it meets the basic nutritional requirements for the animals' maintenance, growth, production, health and reproduction. Qualified dairy nutritionists can assist in formulating rations that economically meet nutritional requirements of animals. Dairy nutritionists can also:

- Check that feed and feed ingredients are carefully mixed and formulated according to the animals' dietary needs using dairy nutrition models
- Adjust rations to ensure the correct content of protein, energy, fiber, macro-minerals and micronutrients in feed whenever forages are changed
- Periodically assess dry matter intake
- Adjust diets to provide for production level
- If conditions warrant, check homegrown or purchased feed ingredients and commodities for nitrates, mycotoxins and other soil or climate-induced problems
- Check feed quality to see if it matches the manufacturer's statement

Animals should be provided feed on a continuous basis with new feed delivered several times daily or replenished through a push-up process.

Daily removal of non-consumed feeds ensures feed freshness, prevents mold and spoilage, and aids in insect control. This is a particularly important practice with high-moisture feeds like silage. A smooth feeding surface will enhance cleaning and routine sanitation of eating areas as refused feed is removed.

Safely storing bulk supplies of feed in appropriately designed areas will help avoid moisture, vermin and bacterial or fungal contamination. Proper storage will also help assure maintenance of feed quality and safety. As a best practice, **medicated feeds are stored separately and properly labeled.** Store toxic compounds outside of the feed storage area and outside of the animals' resting area.

Mycotoxins are secondary fungal metabolites that are toxic to animals and humans. Mycotoxin-producing molds are ubiquitous in nature and thus mycotoxin contamination of feeds is a potential consequence of normal mold plant interactions. Mycotoxin-related economic losses include reduced milk production, poor fertility, potential contaminated milk and increased disease susceptibility.

Feed Management

Protection from Heat and Cold

✓ **All age classes of animals are protected from heat and cold for typical climatic conditions.**

Environmental temperature affects an animal's thermal comfort, which in turn, affects an animal's behavior, metabolism and performance. The temperature that the animal experiences and the effect on the animal is the net result of air temperature, humidity, air movement, shade, insulating effects of the surroundings and the animal herself.

The thermoneutral zone (TNZ) is the range of temperatures between which the animal does not need to expend energy to stay warm or to cool. The TNZ for newborn calves is 50°-78° F; for month-old calves and adult cattle the TNZ is typically 32°-73° F. Except for newborn calves, cattle are quite cold tolerant. However, compared to humans, cattle become heat stressed at lower temperatures. To account for the impact of both temperature extremes and relative humidity, use the Temperature Humidity Index (THI) and begin heat abatement measures at a THI of 65°-72°.[1,2] Cold abatement should be provided promptly for calves starting at a THI below 50° and for adult cattle below 32°.

Heat Abatement

Monitoring cows' respiratory rates is the best way to determine if they are under heat stress. If 8 of 10 cows have respiratory rates of 60 beats per minute (BPM) or above, the group is suffering from heat stress.

A cow in severe heat stress can show respiration rates as high as 120 and 140 BPM and a rectal temperature exceeding 106° F.

With any amount of heat stress, milk yield losses are experienced and reproductive losses are detectable.

Under heat stress conditions, farmers should implement heat stress mitigation strategies.

These strategies may include:

Drinking Water

Cattle must have sufficient water access to meet their intake needs under heat stress conditions, which may exceed 30 gallons per cow per day for high-yielding cattle.[3] Within housed conditions, at least two waterers are recommended per group with at least 2 inches of accessible trough perimeter per adult cow. Water troughs must also refill quickly for animals to continue drinking. Water flow should be at least 2.6 gallons per minute for bowls and 5-7 gallons per minute for troughs.

Shade

Cattle will readily use shade when solar radiation increases. Animals should have access to shade that allows for simultaneous use by the entire group to minimize competition.

Air Movement

Air movement speeds of 200-400 feet per minute are ideal for optimal cooling. To supply this fast-moving air in holding areas, pens and under shades, farmers can use mechanical ventilation systems like tunnel and cross ventilation or supplemental recirculation fans.

Soaking and Misting

Water can be used to cool the air before it reaches the cow. Evaporative cooling pad systems are one way to accomplish this. Water may also be used to enhance evaporative cooling by soaking the cow herself, often coupled with the application of fast-moving air over her skin. The parlor holding area is a priority area for cooling on most dairy farms.

Cold Abatement

Cattle facing cold conditions, especially calves, should be provided with adequate feed to maintain

Heat Stress: Factors & Management Tips

FIGURE 3

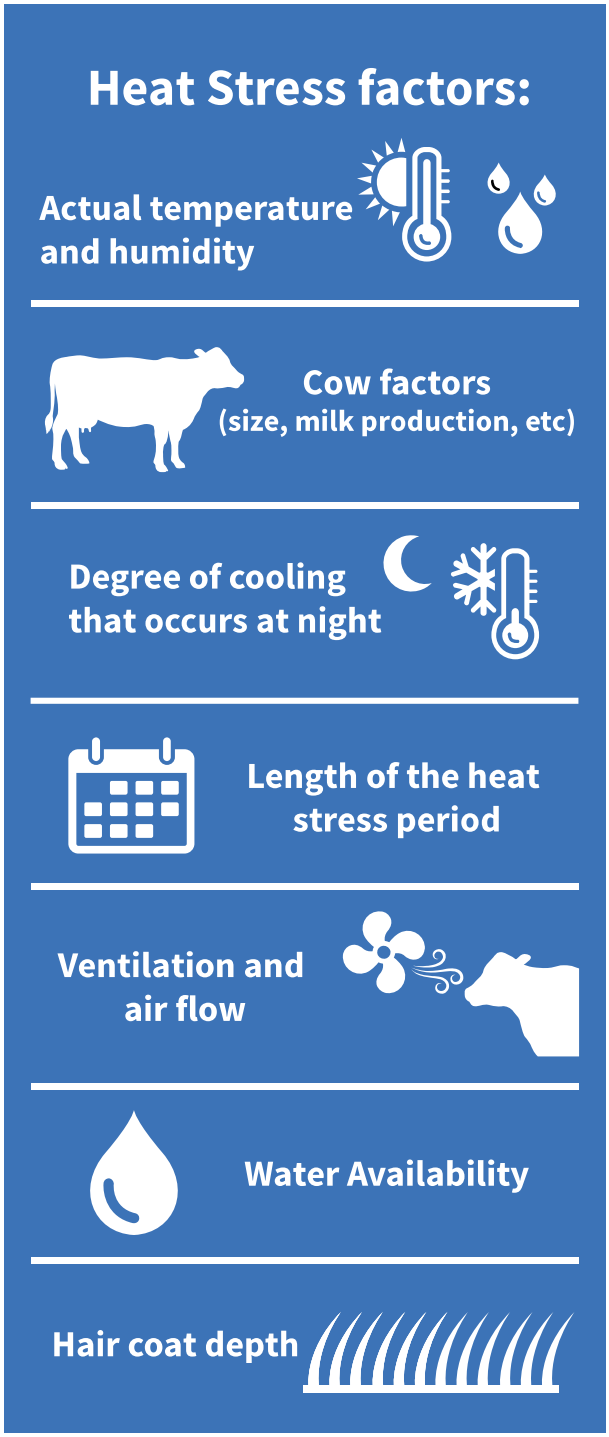
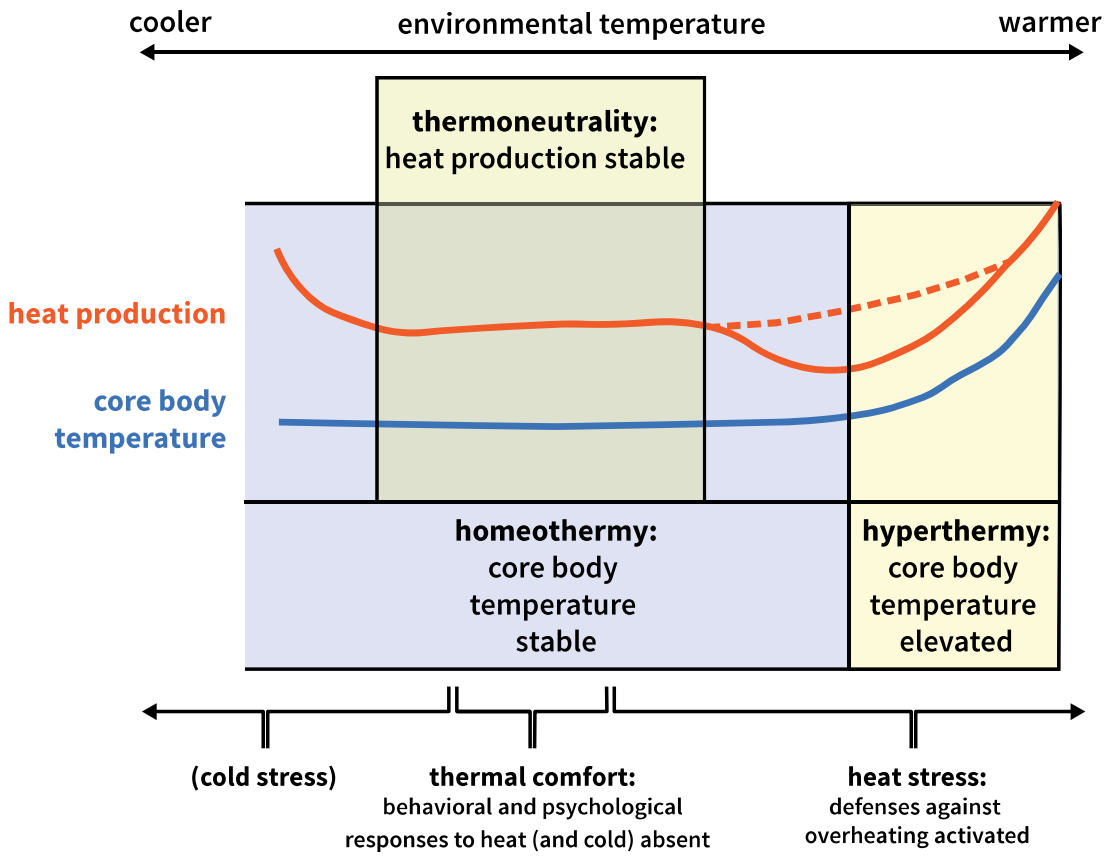


FIGURE 4

Source: Alltech (alltech.com/dairy-on-farm-support/resources)

FIGURE 5: Effects of Heat and Cold Stress



Source: "Considerations for Cooling Dairy Cows with Water" Jennifer M.C. Van Os, PhD

body condition along with wind and moisture protection.

Cold abatement strategies may also include:

- Curtains
- Windbreaks
- Barns/sheds
- Additional bedding

It is important to shield a calf under 1 month of age from drafts, which typically are defined as air speeds of more than 50 feet per minute. The pre-weaned calf prefers dry bedding which is essential in cold weather climates. Consider higher milk feeding rates to supplement calories for growing calves and a deep bed of straw to allow for nesting. Clean calf jackets may also be used to supplement these strategies.

Housing

✓ **All age classes of animals have housing that allows for the ability to easily stand up, lie down, adopt normal resting postures and have visual contact**

with other cattle without risk of injury.

- ✓ **All age classes of animals have a resting area that is clean, dry, provides traction at all times when away from the milking facility and does not pose risk of injury.**
- ✓ **All age classes of animals have a method of daily exercise (weather permitting, if outdoors).**

Cattle of all ages should be able to stand up, lie down and adopt normal resting postures within a given housing system. Factors that can affect these behaviors include the lying area surface, size and configuration.

Dairy cattle are highly motivated to spend time lying down and have been shown to reduce feeding time in order to secure a lying space.[4,5] Therefore, it's important to provide a resting area that is clean, dry, provides traction at all times when away from the milking facility and does not pose risk of injury.

Lying Area

Cattle have increased lying time in well-bedded environments, which reduces the risk for lameness.[6,7] The most important indicator of an insufficient lying surface is the presence of hock injuries. Cows kept on deep, loosely bedded stalls of sand or dried manure solids, for instance, consistently have fewer hock injuries than those kept on sparsely bedded surfaces.[10] In addition, appropriate bedding materials and manure removal help control mastitis. Bedding should be smoothed and groomed as often as is necessary to keep the surface clean, soft and dry.[11] Regardless of lying area surface, lack of adequate bedding reduces lying time and increases the risk of lameness and injuries .[12,13,14,15]

Bedding should be dry in best practice. Several research studies provide strong evidence that cattle spend less time lying down in wet bedding or mud and will avoid wet surfaces if given a choice.[16] Dryness is also important for bedding to provide insulating properties, which is particularly important for young calves in cooler weather. Dairy calves also show a clear preference for drier bedding and aversion to concrete lying surfaces, indicating that access to dry bedding is also important for growing calves.[17]

The lying area should be 1 to 2 feet higher than the pen surface and located under the pen shades, if used. Daily grooming is necessary if cattle cooling systems are used under the shade. A best practice is to provide bedding under the shade during extreme cold or wet conditions. Current recommendations for freestall design and space provision for heifers and mature cows are provided in **Tables 2 and 3** (see pages 36 and 37).

Social Environment

Cattle are herd animals. Socially isolated cattle show signs of stress:

- Increased heart rate
- Vocalization
- Defecation/urination
- Heightened cortisol levels[8,9]

As a best practice, minimize isolation and maintain visual contact with other animals. The only exception is when cows approach calving.

The tables and images on the following pages provide recommended guidance for space requirements of animals in various housing systems.

size of future herd members, and cattle behavior when using stalls. Sufficient space should exist for

TABLE 2: Recommendations for lying space requirements by estimated body weight for bedded pack housing of **adult cows.**

ADULT COWS

Stall Dimensions (inches)	Body Weight Estimate (lbs)					
	1000	1200	1400	1600	1800	2000
Center-to-center stall divider placement (stall width) **(A)**	42	45	48	50	54	57
Total stall length facing a wall **(B1)**	96	108	108	120	120	126
Outside curb to outside curb distance for head-to-head platform **(B2)**	180	192	192	204	204	216
Distance from rear curb to rear of brisket locator **(C)**	64	66	68	70	72	75
Width of rear curb **(D)**	6-8	6-8	6-8	6-8	6-8	6-8
Horizontal distance between rear edge of neck rail and rear edge of curb for mattress stalls **(E)**	64	66	68	70	72	75
Horizontal distance between rear edge of neck rail and rear edge of curb for bedded stalls **(E)***	58	60	62	64	66	69
Distance from rear edge of divider loop to point of curb **(F)**	9	9	9	9	9	9
Height of brisket locator above top of curb (loose bedded stall or mat/mattress surface) **(G)**	3	3	4	4	4	4
Height of upper edge of bottom stall divider rail above top of curb (loose bedded stall or mat/mattress surface) **(H)**	10	10	12	12	13	14
Interior diameter of the stall divider (loop) **(I)**	30	33	33	36	36	36
Height of neck rail above top of curb (loose bedded stall or mat/mattress surface **(J)**	42	45	48	50	52	54
Obstruction height **(K)**	5-35	5-35	5-35	5-35	5-35	5-35
Horizontal distance from brisket locator to loop angle **(L)**	20-22	20-22	20-22	20-22	20-22	20-22
Rear curb height **(M)**	8	8	8	8	8	8

**E in deep, loose-bedded stalls is less than in mattress stalls to encourage cows to stand with rear feet in alley instead of on stall base. From The Dairyland Initiative:* thedairylandinitiative.vetmed.wisc.edu

TABLE 3: Recommendations for lying space requirements by estimated body weight for bedded pack housing of **heifers.**

HEIFERS

Weight (lbs)	<130	135	220	330	440	660	880	1100
Bedded resting area per animal in square feet	35	35	35	35	35	40	50	60

From The Dairyland Initiative: thedairylandinitiative.vetmed.wisc.edu

each animal to lie down without disturbance from neighbors, and stalls should be designed to allow for the normal rising and lying movements of the cow. Unobstructed lunge space is essential to allow cattle to complete the normal rising movement.

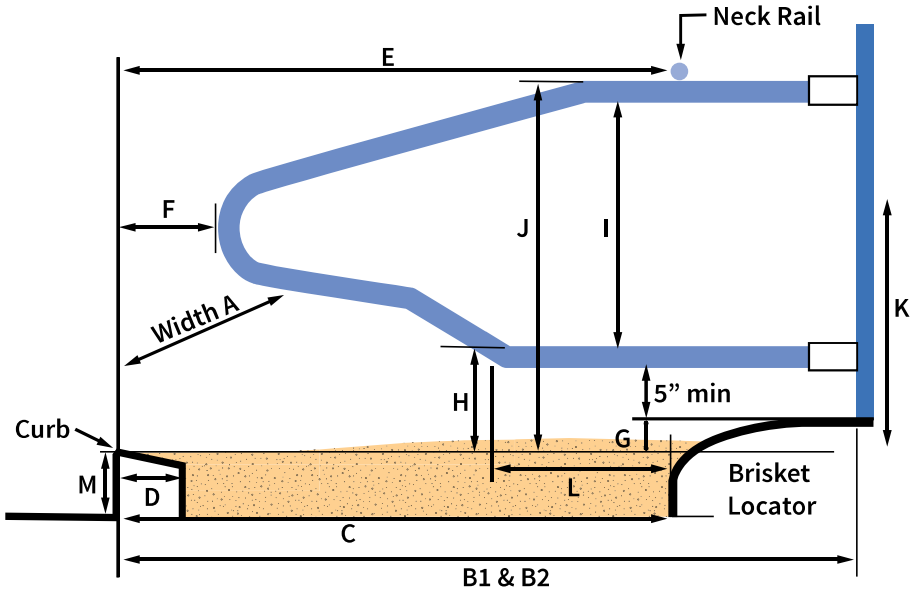
Longer stalls improve leg health and cows spend more time lying down in wider stalls.[18,19] Stall dimensions (stall width, brisket boards and neck rail placement) and tiestall chain length should be set to maximize cow comfort and lying area use.

Keeping a tiestall clean should not mean sacrificing the ability for cows to use the stall for lying and standing. Less restrictive neck rails that are further from the curb and higher allow for the cow to move fully into the stall and have been shown to reduce lameness.[20]

Space Allowance

In loose housing systems, increased cow density in the pen increases competition among cows for access to feed,[21] stalls[22] and water. Cattle

FIGURE 6: Stall Dimensions for Lying Space Requirements



From The Dairyland Initiative: thedairylandinitiative.vetmed.wisc.edu

management must accommodate these challenges so that all animals within a pen receive adequate nutrition and water without competitive pressure. In best practice, all animals should have access to a sanitary and comfortable place to rest and eat at any given time.

The implications of overstocking barns are complex. In studies where only the number of freestalls are changed and feeding space is held constant, lying time is always reduced when there are fewer stalls than cows. However, on farms where stocking density affects both the number of stalls available and feeding space, overstocking is not an important predictor of lying time but does increase feeding rate.[23]

Exercise

Regardless of age, all animals should be in an environment where they're able to turn around or locomote each day.

Exercise for tied animals provides opportunities for grooming the back of the body, social grooming and walking/trotting.[24,25] Controlled studies show that exercise may also improve hoof health. [26,27]

Exercise area quality is important and, in best practice, minimizes any risk for injury. Tied cattle should have daily exercise (weather permitting, if outdoors) in an area that is clean, dry and of appropriate flooring material.

Facility Design

Flooring

✓ **Facilities are designed to prevent injuries, slips and**

falls of animals.

Concrete flooring surfaces should be appropriately grooved or textured to reduce the risk of animals slipping, which can result in injuries, and should be designed such that they do not cause injury. Skid-resistant surfaces reduce injuries and must retain their non-slip characteristic after cleaning, scraping or wear.

High-traction, rubber flooring is desirable in areas of the facility where cows stand for prolonged periods (i.e., holding area), in transfer lanes to reduce hoof wear and in other areas to reduce the risk of slipping and injury. Plans should exist to minimize the impact of seasonal changes that reduce traction, like ice. It is essential for all maternity areas to have high-traction flooring given the increased number of standing periods during labor.[28]

Electrical Currents

✓ **Facilities are designed to prevent unnecessary contact with electrical currents.**

Crowd gates, electrical fences and stall trainers are among the many sources of electrical currents on farm. Ensuring the proper functioning of equipment with electrical current reduces the chances of negative animal care and health events. Tools should be regularly and appropriately adjusted, maintained and correctly located, so that cows are not subject to continuous electrical current. Stray voltage checks are also valuable as stray voltage can cause behavior changes and milk production loss.

Lighting

✓ **Facilities are designed to have adequate lighting for animal observation and family and non-family employees with animal care responsibilities safety.**

Lighting should allow inspection of animals by family and non-family employees and provide safe working conditions.

In facilities where animals are routinely observed or handled, like for milking or estrus observation, lighting should be evenly distributed. An outdoor light attached to a corral or building where animals congregate provides sufficient illumination for safety purposes.

Air Quality

✓ **Facilities are designed to provide proper ventilation in all housing facilities that reduces odors, dust and/or noxious gas.**

Air quality can be improved through manure management and good air movement provided by well-designed natural or mechanical ventilation systems. Adequate ventilation helps prevent respiratory and other diseases by removing heat, microbes, water vapor, air pollutants and odors from an enclosed animal facility and replacing contaminated air with fresh air.

Ventilation also modifies the indoor air temperature, so supplemental heating and cooling may be needed when temperature control is critical. Effective barn ventilation will provide a minimum of four air changes per hour in the winter and 40-50 air changes per hour in the heat of the summer.

The risk of infection from airborne pathogens may be minimized by segregating or isolating animals with highly contagious diseases from the air space occupied by the rest of the group/herd, and by ensuring adequate ventilation rates. As a best practice, ensure the ventilation system does not move air from infected animals to areas occupied by healthy animals.

Emergency Preparedness

✓ **The facility has names, telephone numbers and the site address posted in a prominent location, in the languages understood by family and non-family employees with animal care responsibilities, for**

emergency preparedness.

Time is of the essence in emergency situations. Telephone numbers of emergency contacts (e.g., herd manager, owner, veterinarian, site address and co-op/processor) should be posted in a prominent place in the animal facility. The posting should be in employees' native languages to enhance communication and response time.

Emergencies can range from significant weather events to unexpected absences. Routine walk-throughs of emergency action plans with all involved individuals can help everyone understand their respective roles and ensure the emergency is managed as intended.

✓ **The facility has a written emergency action/crisis plan to effectively manage emergencies or crises that may occur.**

Animal caretaker or temporary help arrangements should be made to cover emergencies, weekends, holidays and unexpected absences of assigned animal caretakers. All animal caretakers, including temporary help, must be informed of animal care expectations and qualified to perform assigned duties.

Emergency communications can be sped up by posting the names and telephone numbers of emergency contacts (e.g., herd manager, owner, veterinarian, site address, equipment dealers and power company) in a prominent place in the animal facility in employees' native languages.

Emergency action plans should include:

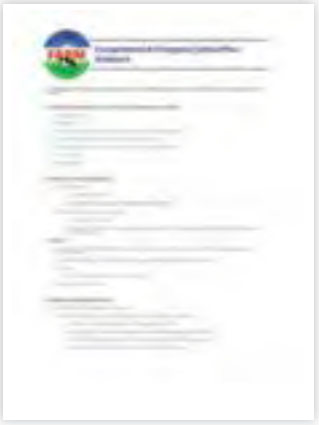
- Identification of potential emergency situations
- The following components for each potential emergency situation:
  - Actions to take for the situation
  - Designated people in charge of performing actions
  - Individuals given authority to perform specific action when emergency occurs
  - Communication flow for quick and accurate information sharing
  - Data and information related to: site, utilities, evacuation routes, road conditions, equipment/materials involved, injuries and locations of resources
  - Emergency supplies and equipment
  - Training and training documentation on the execution of the emergency plan for all involved, including employees and first responders
  - Response scenario options
  - Sheltering in place

Review the Comprehensive Emergency Action Plan Guidance in the **FARM Resource Library.**

EXAMPLE RESOURCES

Emergency Contact — Poster

Emergency Contact — Magnet



Emergency Action Plan

Visit **nationaldairyfarm.com** for free forms and other resources.

Appendix 4

05

Animal Management

Management Checklist

Herd Health Plan & Protocols

- ✓ All written protocols are translated into languages understood by family and non-family employees with animal care responsibilities.
- ✓ The written herd health plan includes an effective written protocol for treatment of the following common diseases:
  - *Mastitis*
  - *Metritis*
  - *Metabolic diseases of milk fever, ketosis and displaced abomasum (DA)*
  - *Pneumonia, diarrhea and any additional routinely occurring diseases identified by the veterinarian*
- ✓ The written herd health plan includes an effective written protocol for vaccinations that specifies:
  - *Age(s) when vaccination given*
  - *Product used*
  - *Dosage administered*
  - *Route of administration*
  - *Withdrawal times*
- ✓ The written herd health plan includes an effective written protocol for lameness prevention and treatment.
- ✓ The facility has an effective written protocol for milking procedures.
- ✓ The written herd health plan includes an effective written protocol for managing difficult calvings (dystocia).
- ✓ The written herd health plan includes an effective written protocol to manage pests.
- ✓ The written herd health plan includes an effective written protocol to manage flies.
- ✓ The written herd health plan includes an effective written protocol to manage parasites.
- ✓ The facility has an effective written protocol to manage biosecurity.

Castration

- ✓ Bulls being raised as dairy steers are castrated at earliest age possible.
- ✓ Pain mitigation for castration is provided in accordance to the signed protocol by the Veterinarian of Record.
- ✓ The written herd health plan includes an effective written protocol for castration.

Branding

- ✓ Cattle are branded at the earliest age possible.
- ✓ Pain mitigation for branding is provided in accordance with the signed protocol by the Veterinarian of Record.
- ✓ The herd health plan includes an effective written protocol for branding.

Animal Management Observations

- ✓ Each animal is permanently identified.
- ✓ The facility complies with the ban on routine tail docking.

Outcomes-Based Animal Observations

- ✓ 99% or more of pre-weaned calves (>2 days old), post-weaned heifers and lactating cows observed have a body condition score of 2 or greater on FARM body condition scorecard.
- ✓ 95% or more of lactating cows observed do not have broken tails.
- ✓ 90% or more of pre-weaned calves (>2 days old), post-weaned heifers, pre-fresh heifers/dry cows and lactating cows observed score 2 or less on the FARM hygiene scorecard.
- ✓ 95% or more of the lactating cows observed score 2 or less on the FARM knee scorecard.
- ✓ 95% or more of the lactating cows observed score 2 or less on the FARM hock scorecard.
- ✓ 95% or more of the lactating cows observed score 2 or less on the FARM locomotion scorecard.

Herd Health Plan & Protocols

✓ **All written protocols are translated into languages understood by family and non-family employees with animal care responsibilities.**

Use written protocols to train family and non-family employees, and ensure job responsibilities are performed as intended. Protocols should provide enough detail to ensure that employees are empowered to implement their job responsibilities consistently and accurately. To ensure the best understanding of job expectations, protocols should be translated into languages understood by those with animal care responsibilities. Written protocols can use images or other learning tools to enhance the understanding of the protocol's content.

Common Diseases

✓ **The written herd health plan includes an effective written protocol for treatment of the following common diseases:**

- *Mastitis*
- *Metritis*
- *Metabolic diseases of milk fever, ketosis and displaced abomasum (DA)*
- *Pneumonia, diarrhea and any additional routinely occurring diseases identified by the veterinarian*

An effective herd health plan emphasizes prevention, rapid diagnosis and quick decision making on the necessary treatment of all sick animals. A licensed veterinarian should help dairy farmers develop and implement a herd health plan.

Vaccination

✓ **The written herd health plan includes an effective written protocol for vaccinations that specifies:**

- *Age(s) when vaccination given*
- *Product used*
- *Dosage administered*
- *Route of administration*
- *Withdrawal times*

A very important component of antimicrobial stewardship is prevention of disease. Vaccinations can help prevent or reduce disease effects, which ultimately can decrease the need for antimicrobial therapy. The VOR is the ideal resource to assist the farm with developing a vaccination protocol. The protocol should include the type of vaccine to use, vaccine storage and administration.

In general, a basic vaccination program should be used on every farm to enhance immunity to disease. Further vaccination strategies can be implemented based on the veterinarian's knowledge of the herd's disease history and farm risk.

Lameness

✓ **The written herd health plan includes an effective written protocol for lameness prevention and treatment.**

Lameness is caused by painful lesions to the limb or foot and compromises animal welfare. Lameness interferes with normal resting behavior, movement to and from the milking area, and feeding activity. Lameness also limits the expression of estrus and influences general health.

Lameness should be a management priority for all dairy herds. Foot lesions most associated with dairy cattle lameness include infectious diseases like digital dermatitis (hairy heel wart) and foot rot, as well as non-infectious diseases like white line lesions and sole ulcers.

Lameness may be reduced by:

- Routine surveillance for lame cows coupled with prompt, effective treatment
- Routine use of foot baths
- Improved flooring
- Providing adequate time for daily rest by minimizing time out of the pen to less than three hours per day
- Avoiding overstocking
- Maintaining thermoneutral zone
- Preventive hoof trimming

Milking Procedures

✓ **The facility has an effective written protocol for milking procedures.**

Appropriate animal handling at milking is important for both animal well-being and productivity. Numerous studies have found that farms with quiet, confident animal caretakers have higher milk production. All animal caretakers with milking responsibilities should behave in a calm and controlled manner throughout the milking process. Milkers should be trained to load cows into the parlor in accordance with the stockmanship principles outlined in Chapter 3.

Specifically:

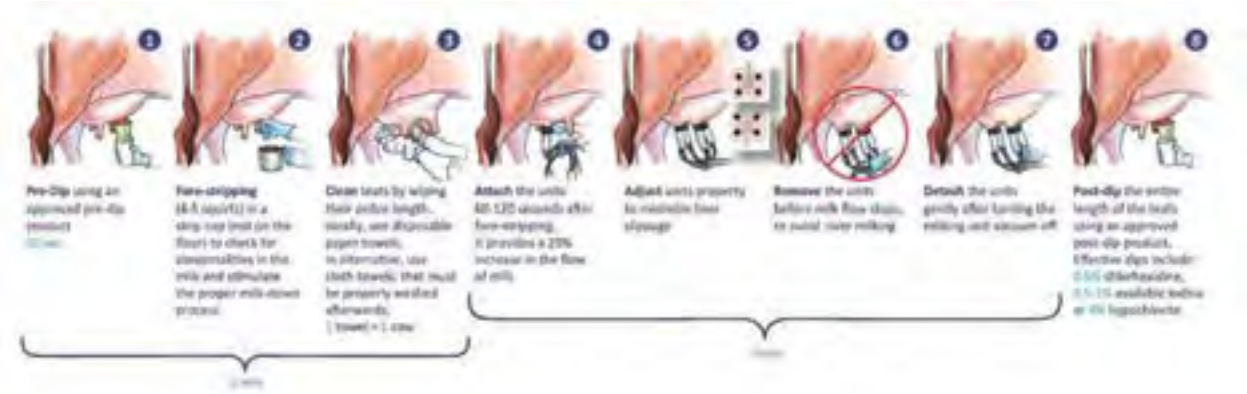
- Cows should be moved without excessive vocal or physical interaction, resulting in calm parlor movement.
- Animal handlers should walk against the flow of cows coming into the parlor, paying attention to the reaction of the cattle and adjust for balking or stopping. To return to their starting positions, animal handlers should use a path that does not impede the flow of cattle movement.
- Gates and restraining equipment should operate smoothly, quietly and safely.

Ideally, the total time out of the pen for each milking should be less than one hour for the last cow milked. On farms with a parlor, the pre-milking holding area is typically the place of highest animal density on the farm and should be a focus for prevention of injury as well as cow comfort and movement. The design of the holding area's flooring, space, sidewalls and entrance to the milking parlor should take these factors into account. Animal comfort can be ensured in holding areas and the milking parlor by using fans, sprinklers or other technology to moderate temperature extremes.

The preparation routine that signals the beginning of milking should be consistent and as low stress to the cow as possible. The routine should include checking for abnormal milk, and thorough cleaning and drying of the teats. Avoid medical examinations or unpleasant experiences being associated with the place of milking.

Milking equipment should be regularly maintained and checked for vacuum level, pulsation rate and pulsation ratio. To prevent disease transmission, milking equipment must be maintained, cleaned and sanitized. Teat ends should be periodically inspected to facilitate timely identification of equipment problems.

FIGURE 7: Example Milking Procedure



Source: Best Dairy Farming Practices, published by SAFOSA

Difficult Calvings

✓ **The written herd health plan includes an effective written protocol for difficult calvings (dystocia).**

Dystocia is a difficult birth typically requiring assistance from the animal caretaker. The facility must have a herd health plan including an effective written protocol for animal caretakers to handle difficult calvings. The protocol should include items like when to intervene and what is appropriate equipment to use when assisting an animal that is experiencing a difficult calving.

Pest, Flies and Parasite Control

✓ **The written herd health plan includes an effective written protocol for pest control, flies and parasites.**

Pest, parasite and fly control are part of a thorough herd health program because they transmit diseases and interfere with animal comfort.

Exercise caution to avoid contaminating feedstuffs when implementing pest control, as contaminants may pass into the animals' bodies and milk. A certified pesticide applicator or a pesticide service may be used. Read and follow label directions for all pesticide products.

Biosecurity

✓ **The facility has an effective written protocol for biosecurity[1].**

A biosecurity protocol helps prevent exposing cattle to diseases that may be transmitted from other animals, humans, vehicles or additional external sources. Sound biosecurity protocols allow for a dairy operation to maintain business continuity and animal health and well-being.

A biosecurity protocol may include processes around:

- Cleaning and disinfection
- Vehicles and equipment
- Personnel
- Animal movement
- Product movement
- Carcass disposal
- Manure management
- Parasite, pest and fly control
- Feed

Castration

✓ **Bulls being raised as dairy steers are castrated at earliest age possible.**

✓ **Pain mitigation for castration is provided in accordance to the signed protocol by the Veterinarian of Record.**

✓ **The written herd health plan includes an effective written protocol for castration.**

Castration is performed to prevent unwanted mating by stopping the production of male hormones and semen. In addition, castration produces cattle that are less aggressive and easier to handle, which promotes animal and human safety. Bulls being raised as dairy steers should be castrated at the earliest age possible.

There is scientific evidence that castration is acutely painful regardless of the method used. While obstacles to immediate implementation exist, research suggests that application of local analgesics have the potential to minimize or eliminate pain and stress associated with castration.

The most common methods of castration are surgical, banding and Burdizzo (physical crushing of the cord). Farmers should consult their veterinarian to determine the right methods of castration and pain management.

Although banding results in minor discomfort at

the time of castration, numerous studies have found that cattle show signs of pain for up to several weeks following the application of the band or ring. Surgical and Burdizzo castration may be better options from an animal care perspective. The advantage of these two methods is that pain can be minimized by providing immediate pain mitigation at the time of surgery as well as post-operative analgesia.

Branding

- ✓ **Cattle are branded at the earliest age possible.**
- ✓ **Pain mitigation for branding is provided in accordance with the signed protocol by the Veterinarian of Record.**
- ✓ **The written herd health plan includes an effective written protocol for branding.**

In some cases, branding is required by state law or is used to prevent theft and identify ownership. A facility's herd health plan should include a written protocol for branding if it is conducted at the facility. Cattle should be branded at the earliest age possible. Brands must never be applied to the face. Pain mitigation should be provided in accordance with the signed protocol by the VOR.

Little is known about how to alleviate the pain associated with hot iron and freeze branding, although freeze branding has been shown to be less painful.[2] Recent research has shown that wounds incurred from branding are immediately painful regardless of anesthetics or non-steroidal anti-inflammatory drugs (NSAIDS) used at the time of procedure and remain painful for at least eight weeks afterwards.

Under best practice, farms should work with their veterinarian to evaluate the necessity of branding, opting to use other forms of identification such as tamper-proof radio-frequency identification (RFID) if possible.

Animal Management

Observations

- ✓ **Each animal is permanently identified.**

Animal identification and record keeping are critical for making important management decisions about feeding, grouping, selecting, treating, breeding and culling an animal from the herd. In addition, food safety, foreign animal disease threats and bio/agro-terrorism concerns make premise and individual animal identification a necessity.

In 2012, the U.S. Department of Agriculture (USDA) finalized the Animal Disease Traceability (ADT) rules establishing general regulations for improving the traceability of U.S. livestock moving between states. Under the ADT final rule, all dairy cattle females, regardless of age, and all male dairy cattle, including dairy steers born after March 11, 2013, are required to be officially identified by a device or method approved by USDA[3] prior to interstate movement. The FARM Program recommends using 840-RFID ear tags[4] , which USDA recognizes as an official identification device for the lifetime of an animal.

Other acceptable permanent individual animal identification include:

- Brite tags
- Vaccination tags
- Dangle tags
- Button tags
- Tattoo
- Ranch brand with cow number

- ✓ **The facility complies with the ban on routine tail docking.**

The National Dairy FARM Program opposes the routine tail docking of dairy animals, except in the extraordinary case of traumatic injury to an animal. This practice was phased out under FARM Program standards as of January 1, 2017.

Current scientific literature indicates that routine tail docking provides no benefit to the animal or quality of the milk. The AVMA, AABP and the National Mastitis Council all oppose the routine tail docking of cattle. Switch trimming is the recommended alternative.

Outcomes-Based Animal Observations

Making the Switch

Switch trimming is the best management practice a farmer can use to transition away from tail docking. Evaluate the timing and method of the procedure to ensure it meets a farm's individual needs.

There are many switch trimming tools, including hand shears, scissors and clippers. Regardless of method, family and non-family employees should be appropriately trained on how to switch trim.

Successfully transitioning away from tail docking also includes being considerate and aware of cows' full tails.

Areas where additional training should be focused may include:

- Stall, alley, walkway and parlor cleanliness
- Attaching milking units: tails may need to be gently moved to the side to access the udder
- Animal movement around barriers (i.e., gates with latches)

Family and non-family employees should also wear eye protection to protect eyes from any foreign objects, liquids, etc.

Facility management is important to the transition as well. High-quality milk is achievable by following consistent milking procedure protocols. Also, routine cleaning, raking and scraping manure from stalls, alleys, walkways and the parlor during and/or in between each milking time will help maintain cleanliness of animals and facilities.

Source: nationaldairyfarm.com/wp-content/uploads/2018/10/Making-the-Switch_0.pdf

Observing outcomes-based animal measures is the best way to evaluate the care of animals on the farm. Hygiene, locomotion, body condition, hock and knee lesions and broken tails are areas used to demonstrate care. The guidelines that follow are based on review of extensive data in all areas of observation and the opinion of experts in dairy cattle care. Thresholds are set based on consensus among a group of experts and available data. These thresholds and scoring systems are revisited every three years.

✓ **99% or more of pre-weaned calves (>2 days old), post-weaned heifers and lactating cows observed have a body condition score of 2 or greater on FARM body condition scorecard.**

Achieving heifer growth targets and monitoring change in body condition during gestation and lactation are very important. Body condition can change rapidly at and after calving and can be used to guide ration changes. Body condition scoring for dairy cattle is an important management tool for optimizing milk production and reproductive efficiency, while reducing the incidence of metabolic and other peripartum diseases. Heifers and cows overconditioned at the time of calving (BCS > 4) often have lower feed intake and increased incidence of peripartum problems. A BCS loss of more than 1 point during early lactation is excessive and requires farmer and nutritionist attention.

✓ **95% or more of lactating cows observed do not have broken tails.**

The tail must never be used aggressively to move a cow.

Calm and appropriate handling does not harm the animal. Tails can be broken through twisting, jacking or other rough handling. This animal observation is set to detect farm-wide problems in animal handling. The widespread presence of broken tails indicates that there is or has been a handling and stockmanship breakdown. Investigate patterns in tail breaks, consider the age class affected, the location of the breaks within the tail, and observe handling to determine when and how tails are being broken.

✓ **90% or more of pre-weaned calves (>2 days old), post-weaned heifers, pre-fresh heifers/dry cows and lactating cows observed score 2 or less on the FARM hygiene scorecard.**

Proper sanitation and cleanliness helps keep animals dry, clean and free of manure, while also providing them with a comfortable environment. The goals of facility sanitation are to:

- Maintain a clean and dry resting area for the animal
- Minimize animal disease
- Minimize generation of odors and dust
- Minimize pests and parasites
- Minimize spread of pathogens

Basic sanitation practices include keeping facility interiors, corridors and storage spaces clean. Facilities should be free of standing water, excess manure, unnecessary farm items and clutter. Feed and bedding should be clean and dry, even in areas with minimal housing and rainfall. Animal caretakers should also maintain a level of cleanliness to minimize the spread of pathogens.

Open lot facilities may need to be scraped clean and refilled with uncontaminated materials. Removing cattle from an open lot for a short period of time may help eliminate muddy pasture areas.

Regularly remove manure from facilities. Clean walkways and ensure good traction. Standing manure not only impacts udder and leg cleanliness, but it also contributes to lameness problems described within the checklist items that follow.
In best practice, all lying areas should be clean, dry and groomed.

Cleanliness of belly and flank are often an outcome of the dryness of the resting area. Cattle prefer dry lying areas and spend more time resting on dry surfaces.

✓ **95% or more of the lactating cows observed score 2 or less on the FARM knee scorecard.**

✓ **95% or more of the lactating cows observed score 2 or less on the FARM hock scorecard.**

Skin injuries on cattle tend to occur on areas that are in contact with housing elements, with the most common injuries observed on the knees and hocks. These injuries range from a small area of hair loss to open wounds and are sometimes accompanied by infection and swelling of the joint. A healthy hock is free from hair loss and swelling. Skin breakage provides an opportunity for infection to occur, which can lead to swelling, pain and lameness.

A series of studies shows that the risk of hock injuries can be greatly reduced by using deep bedding. Lesions are more common on farms using poorly bedded surfaces like mats and mattresses.[5,6]

✓ **95% or more of the lactating cows observed score 2 or less on the FARM locomotion scorecard.**

Lameness is caused by painful lesions to the limb or foot and compromises animal welfare. Lameness interferes with normal resting behavior, movement to and from the milking area and feeding activity. Lameness also limits the expression of estrus and influences general health.

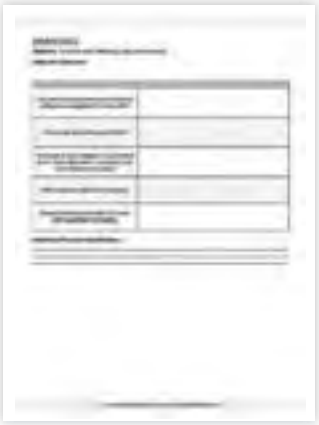
Lameness should be a management priority for all dairy herds. Foot lesions most associated with dairy cattle lameness include infectious diseases like digital dermatitis (hairy heel wart) and foot rot, as well as non-infectious diseases like white line lesions and sole ulcers.

Lameness may be reduced by:

- Routine surveillance for lame cows coupled with prompt, effective treatment
- Routine use of foot baths
- Improved flooring
- Providing adequate time for daily rest by minimizing time out of the pen to less than three hours per day
- Avoiding overstocking
- Maintaining thermal neutral zone
- Preventive hoof trimming

EXAMPLE RESOURCES

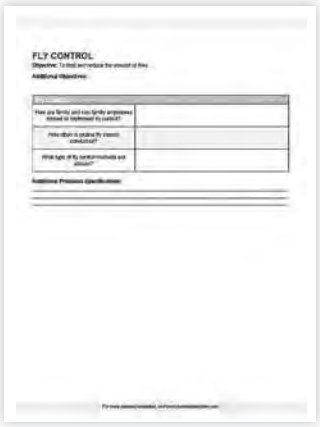
Biosecurity Protocol



Branding Protocol

Castration Protocol

Disease & Illness Treatment Protocol



Fly Control Protocol

Lameness Prevention & Treatment Protocol

Milking Procedure

Parasite Control Protocol

Pest Control Protocol

Vaccination Protocol

Visit **nationaldairyfarm.com** for free forms and other resources.

Appendix 4

06

Antibiotic Stewardship

Appendix 4

Management Checklist

- ✓ The facility adheres to all withdrawal times for milk. All official samples of sold milk have tested negative for antibiotics in the last three years.
- ✓ The facility adheres to all withdrawal times for meat. All meat tissues from animals sent for meat production have tested negative for violative residues in the last three years.

The U.S. dairy industry is committed to producing the highest quality, safe, abundant and affordable milk and dairy beef. Healthy animals help make for safe food, and disease prevention is the key to keeping cows healthy.

When dairy animals get sick and treatment is necessary, farmers and veterinarians use antibiotics and other drugs carefully. Antimicrobials must be used appropriately under veterinary guidance to prevent residues from occurring in milk and dairy beef. The marketing of milk or dairy beef with drug residues, even unintentionally, is illegal and can result in financial and criminal penalties.

Dairy farmers realize the importance of eliminating drug residues in milk and dairy beef. Farmers can take the following steps to mitigate or lessen the chances of antibiotic residues.

FOOD ANIMAL RESIDUE AVOIDANCE DATABANK (FARAD)

FARAD is a university-based national program that serves as the primary source for scientifically based recommendations regarding safe withdrawal intervals of drugs and chemicals in food-producing animals. As such, FARAD is a key resource for protection of our nation's food supply, including milk and meat, against accidental contamination of animal-derived foods with violative residues of drugs, pesticides or other agents that could compromise food safety.

Modern animal agriculture relies heavily on the use of therapeutic drugs, pesticides and other agents that improve overall animal health and promote safe, efficient and humane production practices. Through the assimilation of a comprehensive drug database and the use of state-of-the-art pharmacokinetic modeling, FARAD scientists determine appropriate withdrawal periods for a wide array of chemical entities and provide this information to veterinarians, extension specialists and farmers through a toll-free call center as well as a publicly-accessible website (FARMWeb).

In addition, FARAD provides rapid response assistance regarding extra-label use of drugs in animal agriculture, and during food contamination emergencies which might arise from accidental exposure to environmental toxins, particularly pesticides, or intentional efforts to contaminate the food supply. Finally, FARAD aids in trade matters related to foreign drug approvals and trains future veterinarians in the principles of residue avoidance.

FARAD is a USDA-funded, university-based consortium, which is overseen and operated by faculty and staff within the Colleges of Veterinary Medicine at the University of California-Davis, the University of Florida, Kansas State University, North Carolina State University and Virginia-Maryland College of Veterinary Medicine.

Visit farad.org for more information.

Those steps include:

- Establishing a valid VCPR to ensure proper diagnosis and treatment of disease. The agreement should be reviewed annually with the VOR who makes routine visits to the farm.
- Keeping records of antibiotic use and identifying all treated animals, including treatment protocols.
- Implementing a preventive herd health plan to reduce disease incidence.
- Maintaining milk quality and implementing an effective mastitis management program, including protocol development and review, to reduce the use of antibiotics.
- Implementing family and non-family employee training and awareness of proper animal drug use.
- Using drugs approved for specific disease indications according to labeled recommendations and withdrawal periods. If extra-label drug use is indicated by a veterinarian's prescription, the veterinarian must establish and document appropriate withdrawal periods.
- Not using drugs specifically prohibited for use in milking, dry or growing animals.
- Segregating and milking treated animals after, or in a separate facility from, all non-treated animals to ensure milk is not accidentally combined.
- Using drug residue screening tests specific for the drug used before marketing milk and/or meat from treated animals.
- Not marketing milk and/or culling treated animals when reside status is in question.
- Ensuring antibiotics are stored securely and are monitored for any suspicious activity.

FARM Drug Residue and Prevention Manual

The FARM Drug Residue and Prevention Manual and accompanying pocket guide are educational tools for dairy farm managers on the prudent and responsible use of antibiotics, including avoidance of drug residues in milk and meat.

These tools review antibiotics approved for dairy animals. They can also be used as to help inform on-farm best management practices necessary to avoid milk and meat residues.

Food Armor Program

Food Armor, an organization dedicated to improving antimicrobial stewardship practices in food animal agriculture, teaches residue prevention, food safety principles, responsible drug use practices and antimicrobial stewardship. A team based of food industry professionals, ranging from farmers and veterinarians to packers, processors and food marketers, this broad stakeholder consensus works to deliver a program that translates solid framework into proven on-farm results.

Food Armor offers an online educational platform providing high-quality stewardship education to veterinarians and farmers. Through this self-paced program, learners work to develop habits and use tools to implement antimicrobial stewardship plans.

✓ **The facility adheres to all withdrawal times for milk. All official samples of sold milk have tested negative for antibiotics in the last three years.**

Milk Drug Residue Testing

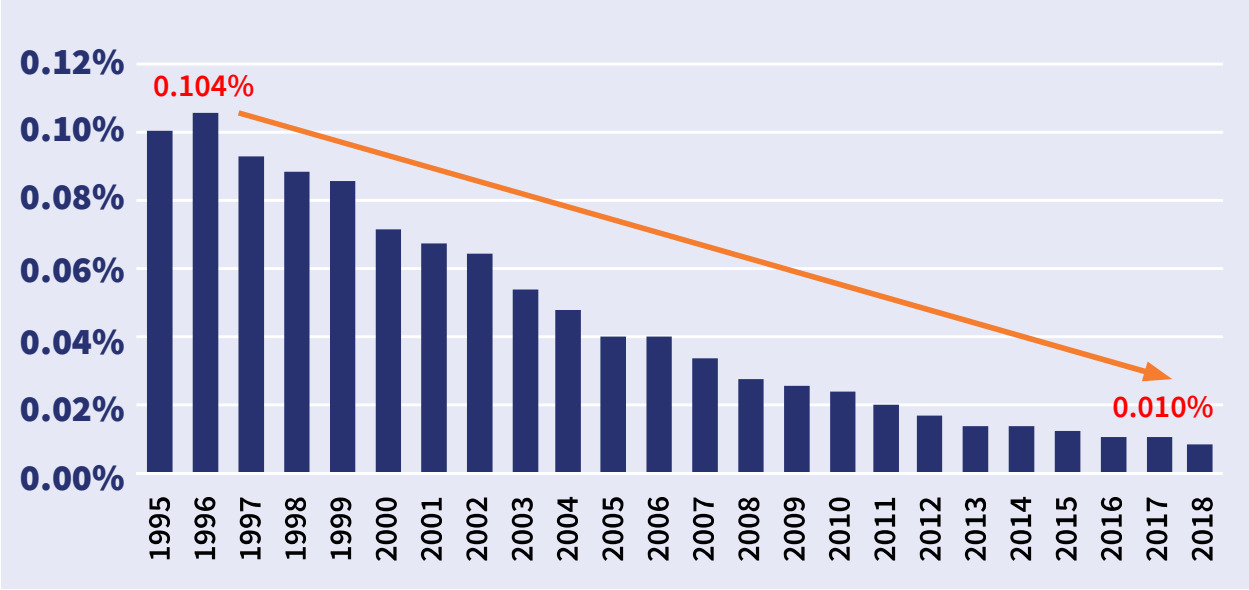
Pasteurized Milk Ordinance (PMO)

The Grade "A" PMO includes the rules that state regulatory agencies use to implement their Grade "A" milk programs, requiring that all bulk milk tankers be sampled and analyzed for beta-lactam drug residues before the milk is processed. The PMO also requires states to test farm-level milk samples at least four times every six months for antibiotics (called Section 6 testing). Most states use an inhibitor test, which shows sensitivity to any antibiotic in milk. Additionally, customers (i.e., processors) may require additional testing for quality assurance purposes. Any tanker found positive for any antibiotic residue is rejected for human consumption.

In 1996, of the 3,384,779 bulk milk pickup tankers tested, 0.104% tested positive[1]. Through increased education and industry advancements, of the 3,572,766 bulk milk pickup tankers tested by industry and state regulatory agencies from October 2018 to September 2019, 0.009% tested positive for drug residues. This signifies a dramatic decrease from an already low level of occurrence.[2]

✓ **The facility adheres to all withdrawal times for**

FIGURE 8: Percent of Bulk Milk Tankers Positive for Antibiotic Residues



meat. All meat tissues from animals sent for meat production have tested negative for violative residues in the last 3 years.

Meat Drug Residue Testing

The U.S. Department of Agriculture Food Safety Inspection Service (USDA FSIS) conducts tests for chemicals — including antibiotics and other drugs, pesticides and environmental chemicals — in meat for human consumption. The USDA FSIS Annual Sampling Program Plan tests for chemicals through a random sampling of tissue from healthy-appearing food animals.

The development of the plan includes:

- Determining compounds of concern for food safety
- Using algorithms to rank selected compounds
- Pairing compounds with appropriate production classes
- Establishing the number of samples to collect

The USDA FSIS Hazard Analysis and Critical Control Point (HACCP) program implemented at slaughter facilities identifies the animals most likely to have drug residues. Animals that display lameness, injection site lesions or signs of illness are targeted for testing.

If there is any doubt about the potential for drug residues in an animal, it should be withheld from market. Each year, about three million adult dairy cows are slaughtered for beef. Of that amount, a very small percentage test positive for a residue. USDA FSIS has reported a 24% decline in the number of tissue residues in market dairy cows during the most recent five years for which data has been released.

USDA FSIS Residue Repeat Violator Lists

The USDA FSIS maintains a Residue Repeat Violator List for Use by FSIS Inspection Personnel[3] that contains the names and addresses of farmers who have more than one meat residue violation in a 12-month period in animals presented for slaughter. Specific information about the violation can also be found in this list, including the plant where the violation was determined, the drug residues identified, and their concentrations and tolerances. Violators listed may have had multiple violations documented in the same processing facility or in separate facilities. This list is intended to aid inspectors in discovering residue tolerance violations before they reach consumers. The USDA FSIS provides a user guide that explains the information contained in the list.

The USDA FSIS also maintains a Residue Repeat Violator List for Use by Livestock Markets and Establishments that contains similar information intended to assist plant owners and operators in identifying residue history of livestock suppliers. This list documents only the source name and address information of repeat violators, so that livestock marketers and buyers may use precaution when marketing and processing animals from listed suppliers. The USDA FSIS provides a user guide that explains the information contained in the list.

Conditions that Warrant Additional Testing at USDA Slaughter Facilities

The following list contains descriptions, directly from USDA documents, of conditions that may warrant testing of carcasses for drug residues:

Mastitis: Signs of mastitis can vary based on the severity and duration of infection and may exhibit varying degrees of clinical signs, from pus-like or discolored discharge from the teats and redness and swelling of the udder, to no visible change in the udder.

Metritis: USDA inspectors will look for this postmortem indication. Be mindful of sending animals to slaughter that show signs of metritis such as high fever, major drops in milk production, or eye or nasal discharge.

Signs of Treatment: Leakage around jugular veins, subcutaneously, intramuscularly or intraperitoneally, or clinical signs indicative of treatment by mouth, such as discoloration from particles found in any part of the digestive tract, are important signs when examining veal calves for testing. Inspectors are aware of common industry practices that could indicate an animal was recently treated. Dairy cows arriving for slaughter with fetlock or ankle bands indicate that the animal has previously received treatment for a medical condition. When observed, inspectors are instructed to determine the appropriateness of additional testing or removal from the food supply.

Peritonitis and Surgery: Signs of recent surgical procedures or findings of surgical devices (e.g., suture, toggles, fistula devices) are only significant if they are associated with active peritoneal or subcutaneous inflammation.

Injection Sites: Live animals and carcasses with lesions or abscesses associated with injections on any part of the animal are of potential concern.

Other Disease Symptoms: Any signs of the following diseases or conditions can lead to an animal being tested for potential chemical residues or to determine fitness for harvest:

- Depression
- An elevated or subnormal body temperature
- Hyperemic skin
- Congested mucous membranes
- Dehydration
- Poor body condition in association with an injury or inflammatory condition, such as abscesses, arthritis, pneumonia, mastitis, metritis or diamond skin

Tolerance Limits

The regulatory tolerances for milk and meat antibiotic residues vary depending on the type of drug used and route of administration. The withdrawal times and tolerances are **only valid if a drug is used according to the label directions and in the class of animal listed on the label.**

If a drug is used in a class of animal not on the label, then there is **NO TOLERANCE** established for that drug and any trace amount, even if it is below the target testing/tolerance level established for the labeled class, is a violation.

Drugs not approved for use in lactating dairy cattle do not have FDA-established tolerances for residues in milk. Further, the tissue tolerances for drugs approved for beef cattle do not apply to lactating dairy cattle. Extra-label drug use if used, must be prescribed by a veterinarian. A complete list of the tolerances can be found in the FDA Green Book[4], which lists all approved animal drugs. Questions or concerns about potential residues or withdrawal times should be addressed with a VOR.

Drugs Not Approved for Use in Food-Producing Animals

The following drugs are **not approved** for use in any species of food-producing animal:

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol (DES)
- Dipyrone
- Gentian violet
- Glycopeptides (example vancomycin)
- Nitrofurans (including topical use)
- Nitroimidazoles (including metronidazole)

Following a thorough literature review, the AVMA, the AABP and the Academy of Veterinary Consultants (AVC) recommend that veterinarians refrain from using aminoglycosides (amikacin, gentamicin, kanamycin and neomycin) in cattle except where approved for use by the FDA, as these antibiotics can cause very prolonged tissue residues.

Extra-Label Drug Use

"Federal law restricts this drug to use by or on the order of a licensed veterinarian."

This statement is on every prescription drug sold. Any use of a drug not specifically listed on the label is called extra-label drug use and is regulated by the FDA under the Animal Medicinal Drug Use Clarification Act (AMDUCA). Using a prescription or over-the-counter drug in an extra-label manner is illegal unless it is specifically prescribed with withdrawal times by a veterinarian working in the context of a VCPR.

Any extra-label use of antibiotics must be used as a prescription and include the written instructions for the specific lifecycle of animals to be treated, including dose, route of administration, frequency of use and withdrawal times for milk and/or meat. Extra-label use generally requires an extended withdrawal time.

Examples of extra-label drug use:

- Changing the dose, such as giving more penicillin than is listed on the label
- Changing the route of administration, such as giving flunixin intramuscularly (IM) or subcutaneously (SQ) instead of intravenously (IV)
- Giving a drug to a different production class of animal, such as using Nuflor® in a lactating dairy cow
- Giving a drug for an indication (disease) not listed on the label, such as using Excede® for diarrhea
- Changing the withholding times, such as not following milk withholding times for fresh cows after dry treatment administration
- Changing the amount of drug per injection site
- Changing the duration of therapy

Milk and Dairy Beef Drug Residue Prevention Reference Manual

The FARM Antibiotic Stewardship module provides ongoing education for the dairy community on the responsible use of antibiotics to keep cows healthy and our milk supply safe.

FARM's **Milk and Dairy Beef Drug Residue Prevention Reference Manual** is the primary educational tool for dairy farms on the judicious and responsible use of antibiotics, including avoidance of drug residues in milk and meat.

Updated each year, the manual and accompanying pocket guide are convenient resources detailing which antibiotics and other drugs are approved for treatment of dairy animals.

8-STEP PLAN FOR SOUND RECORD KEEPING

Step 1: Recommended or Approved Drug List

Make a narrow list of drugs to be used on your dairy with your VOR. The intent is to reduce the scope of drugs used. A short list will permit you to focus your knowledge and will help prevent an accidental violation of antibiotic residue laws.

Step 2: Animal Treatment Plan

When practicing preventive medicine or treating early symptoms of a disease or infection, stay consistent. Establish a treatment plan for your herd health practices to maintain consistency. Review with your VOR and document protocols in the herd health plan.

Step 3: Beginning Inventory

Discard all old drugs and drugs not on your approved drug list (Step 1). Inventory remaining drugs and other appropriate information annually.

Step 4: Record Medicated Feed Purchases

Feeding practices can result in accidental antibiotic residues. Clean feed equipment between batches, and avoid feeding leftover feed from feeder calves, hogs, etc., to lactating dairy cattle.

Step 5: Record of Drug Purchases

Promptly record every purchase of drugs on the day they are purchased. The FDA requires a paper trail of all drugs used on the dairy.

Step 6: Daily Treatment Record

Refer to your daily treatment records before milking or selling market cows. Use the record to properly identify treated cows. Develop good habits to properly manage antibiotics.

Step 7: Monthly Economic Comparison

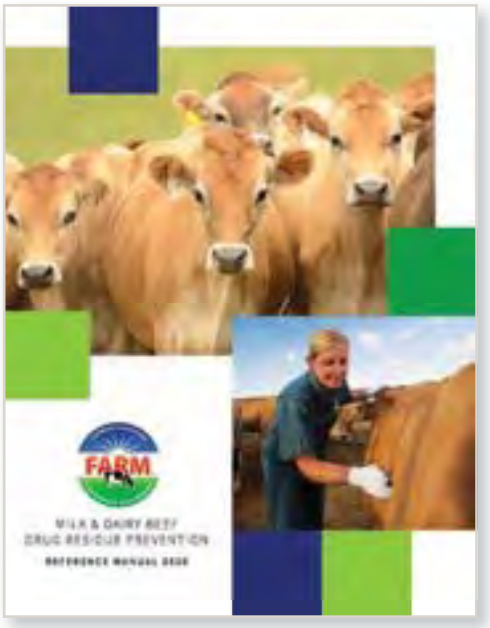
Review the investment you are making in each cow in the milking string on a monthly basis. Review expenses by using the daily treatment records.

Step 8: Disposal

Periodic review of drugs in storage will mean you occasionally throw away drugs that have expired. By recording your daily animal treatments and any discarded drugs, a paper trail of what has happened to all drugs purchased is generated.

This 8-step antibiotic management system may prevent you from incurring a costly and embarrassing antibiotic accident!

EXAMPLE RESOURCES



Milk and Dairy Beef Drug Residue Prevention Reference Manual

Visit **nationaldairyfarm.com** for free forms and other resources.

07

Pre-Weaned Calves

Management Checklist

- ✓ Facilities are designed to have a calving area that is clean, soft, dry, well-lit and well-ventilated.
- ✓ All pre-weaned calves are moved by lifting, walking or the use of clean, properly designed mechanical transport devices.
- ✓ All pre-weaned calves (heifers and bulls) receive colostrum or colostrum replacer within 6 hours after birth, even if immediately transported off the farm.
- ✓ All pre-weaned calves (heifers and bulls) receive a volume of milk or milk replacer to maintain health, growth and vigor until weaned or marketed.
- ✓ All pre-weaned calves (heifers and bulls) are offered fresh, palatable starter feed by day 3 to maintain health, growth and vigor.
- ✓ All pre-weaned calves (heifers and bulls) have access by day 3 to clean, fresh water appropriate for climatic conditions.
- ✓ All calves are disbudded before 8 weeks of age.
- ✓ Pain mitigation for disbudding is provided.
- ✓ The written herd health plan has a written protocol for pre-weaned calf care that includes language specific to areas of pre-weaned calf management.

✓ **Facilities are designed to have a calving area that is clean, soft, dry, well-lit and well-ventilated.**

Recent work indicates that cows prefer social isolation beginning about eight hours prior to calving.[1] A clean, soft, dry, well-lit and well-ventilated calving area has many health benefits for the calf at the time of birth. A separate calving area that is designed to be comfortable, functional and hygienic allows for close observation of the cow and easier, more effective assistance at calving.

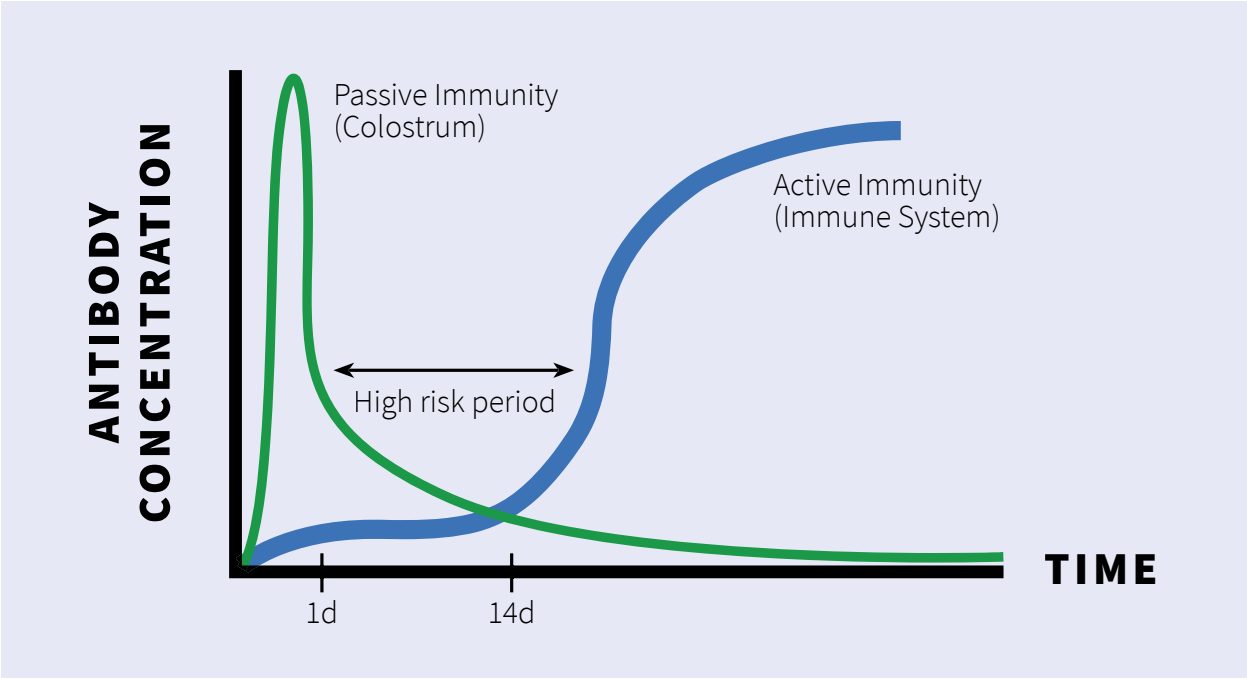
Wet, dirty calving areas foster bacteria that can enter a newborn calf's navel or mouth and create a disease load that overwhelms the calf's naive immune system. A best practice is to clean pens or paddocks between calvings.

✓ **All pre-weaned calves are moved by lifting, walking or the use of clean, properly designed mechanical transport devices.**

Calves should be handled in a calm, controlled and gentle manner. Animal caretakers should receive continuing education or training in animal handling, and the unique ways in which calves should be handled. Calves should be moved by a clean, properly designed transport device such as a calf cart, clean wheelbarrow or similar device with appropriate restraint that ensures calf safety and care. Manual movement of calves is also acceptable and can include walking calves or lifting them from their underside with all four legs gathered. Calf flight zones are different than that of adult dairy cattle and they should be handled with that in mind. Calves should never be dragged, pulled or caught by the neck, ears, limbs, tail or any other extremities, or thrown.

✓ **All pre-weaned calves (heifers and bulls) receive colostrum or colostrum replacer within six hours after birth, even if immediately**

FIGURE 9



Source: Penn State "Feeding the Newborn Calf"

transported off the farm.

Colostrum feeding influences the long-term health and well-being of calves.[2] Calf care and feeding should be based on the counsel of a qualified nutritionist and the herd veterinarian. Calves should receive 4-5 quarts of high-quality colostrum or colostrum replacer (3-4 quarts for smaller dairy breeds) or an amount equivalent to 10% of the calf's body weight in one or two feedings within the first six hours of life.

Monitoring colostrum quality before feeding (e.g., using a Brix refractometer or colostrometer) is considered best practice.[3] Colostrum quality is highly dependent on early harvest. The immunoglobulin G (IgG) content of the colostrum is of high quality if it is over 50 grams per liter. This equates to a Brix value greater or equal to 22%.[4] Colostrum replacements should provide at least 100 grams, 150- 200 grams is preferred, of IgG.

One way to monitor the effectiveness of colostrum management practices is to take calf-side blood samples and measure IgG concentrations. The blood serum concentration of IgG goal should be greater than 10 milligrams per milliliter, or serum total protein greater than 5.5 grams per deciliter, to support positive growth rates and reduced prevalence of sickness and death.

Inadequate colostrum intake results in failure of passive transfer (FPT), which influences calf health and welfare as well future performance as a lactating cow.[5] Dairy farmers should work with their veterinarian to assess FPT.

Esophageal Tube Feeder[6]

Newborn calves are sometimes too weak to suckle or nurse from a bottle. The esophageal tube feeder is an excellent device for feeding colostrum to calves. Proper training on the use, cleaning and sanitation of the feeder is essential for calf health.

The esophageal feeder consists of an esophageal probe, tube, clamp and fluid container. The probe is a rigid or semi-flexible tube made of plastic or stainless steel. It has a tear-shaped end designed to be easily inserted into the esophagus but not into the trachea (windpipe). The esophageal feeder should be thoroughly cleaned to prevent bacterial growth, especially after it has been used for colostrum.

The first step in using an esophageal feeder is to determine the length of tube to be inserted. Measure from the tip of the calf's nose to the point of its elbow, which is the approximate location of the diaphragm. This distance is about 20 inches in most Holstein calves (Figure 10). The proper length can be marked on the tube with a piece of tape. In young calves, only about 20 inches of the tube should be passed into the mouth and down the esophagus (Figure 11).

The tube should first be lubricated by dipping it in the colostrum or milk. A calf will likely suck the end of the tube into its mouth, which makes the tube easier to pass.

Open the calf's mouth by applying pressure to the corner of the mouth or by grabbing over the bridge of the nose and applying pressure to the upper palate or gums. Once the mouth is open, pass the tube slowly along the tongue to the back of the mouth. When the tube is over the back of the tongue, the calf starts chewing and swallowing. The tube should then be passed down the esophagus. A correctly passed tube can be felt in the esophagus; the ball on the end of the tube can be felt easily.

If possible, the calf should be standing before feeding so fluids are less likely to back up and enter its lungs. Calves should be properly restrained for this process.

After the tube is passed and before any liquids are given, the tube should be checked for proper positioning in the esophagus (Figure 12). If it is properly positioned, the rings of the trachea and the rigid enlarged esophagus can be felt easily. Check the exposed end of the tube for spurts of air, which indicate that the tube is in the trachea.

Next, unclip the tube to allow the liquid to drain out of the bag. Hold the bag above the calf or hang it on a nail; it will take several minutes to drain. Liquids should be at body temperature to prevent temperature shock to an already weak calf.

When feeding is over, slowly remove the tube. Clean and sanitize the feeder, and then allow it to drain and dry.

✓ **All pre-weaned calves (heifers and bulls) receive a volume of milk or milk replacer to maintain health, growth and vigor until weaned or marketed.**

After receiving immunity through colostrum or

FIGURE 10: Hyperextension of a calf's neck and points for estimating length of esophageal tube.

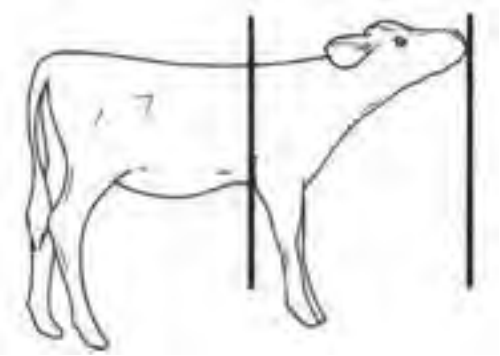


FIGURE 11: Internal view of mouth and esophagus

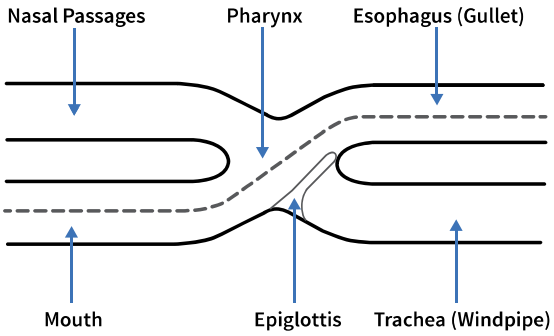
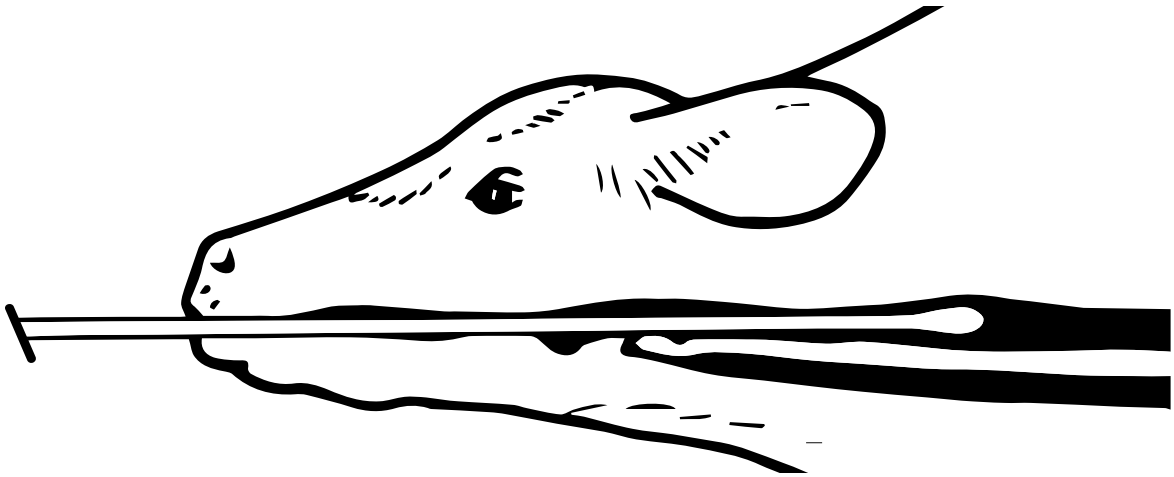


FIGURE 12: Position of esophageal feeder in relationship to the trachea



Source for Figures 10-12: Penn State "Feeding the Newborn Calf" — extension.psu.edu/feeding-the-newborn-dairy-calf

colostrum replacer, calves should be fed milk or milk replacer through weaning. The goal of calf nutrition is to promote healthy, efficient, rapid growth with milk or milk replacer and enhance rumen growth and function by initiating grain intake.

Calves benefit from higher milk/milk replacer intakes during the first four weeks of life when their ability to digest solid feed is limited. Benefits of improved growth and reduced hunger can be achieved by feeding calves more milk or milk replacer.[7]

Calves are motivated to consume large amounts of milk or milk replacer. Holstein calves will drink in excess of 8 quarts or more in two or more feedings per day. Providing an increased volume of milk/milk replacer can lead to earlier breeding ages and higher milk yields later in life.[8] There are no known negative side effects of feeding more milk/milk replacer.

Higher milk intakes will result in looser manure, but this is not associated with increased diarrhea or other health problems. Newborn calves are susceptible to neonatal calf diarrhea (calf scours), especially during their first 28 days of life. Acquired immunity from colostrum is the first and most important control measure for diarrhea.

Feeding only 4 quarts per day of milk or milk replacer equivalent does not allow the calf to meet its nutritional requirements for maintenance, growth and development and is associated with hunger behavior.[9]

Good milk replacer should mix easily in warm water and stay in solution after mixing. Animal caretakers should use the appropriate weight of milk replacer powder volume, temperature, freshness and cleanliness of water to ensure consistency when mixing milk replacers, and use clean feeders.

Take caution if calves destined for sale or slaughter are fed a medicated milk replacer or milk from cows treated with antibiotics. This will prevent problems associated with antibiotic residues in the meat of slaughtered calves. All withdrawal times for medicated feeds must be followed.

✓ **All pre-weaned calves (heifers and bulls) are offered fresh, palatable starter feed by day 3 to maintain health, growth and vigor.**

Introducing small amounts of fresh, palatable, high-quality starter feed by day 3 allows for a calf to meet its nutritional needs and enhance rumen development.

As the calf's body size is expanding in response to milk feeding, it needs more nutrients to maintain itself, which is where starter feed becomes an essential part of the diet. Starter feed fills the nutritional gap between the growing animal and fixed nutrients coming from milk.[10] It is important that calves consume starter early to prepare the rumen in physical size and metabolic activity to be able to sustain on dry feed post-weaning. Starter feed should be replaced daily to maintain freshness and feed intake.

✓ **All pre-weaned calves (heifers and bulls) have access by day 3 to clean, fresh water appropriate for climatic conditions.**

Calves should have access to clean, fresh water by day 3 of life to maintain proper hydration. The proper quantity and quality of colostrum/colostrum replacer and milk/milk replacer must also be provided. Feeding free-choice water to pre-weaned

calves has been proven to improve rate of gain from birth to weaning by 33% compared to calves receiving no water.[11] Additionally, calves receiving daily water changes have been shown to have a 5% weight gain advantage compared to calves whose water was changed once a week.

Feeding milk or replacer should not be a substitute for water. When milk is consumed, it goes directly to the abomasum, bypassing the rumen via the esophageal groove, while water goes into the rumen. Without water in the rumen, rumen development slows dramatically.[10] Free-choice water intake is essential for proper rumen function and for early intake of dry feed.

In cold weather, feed water that is close to a calf's body temperature of 102° F and provide water amounts close to their predicted consumption.

✓ **All calves are disbudded before 8 weeks of age.**

Horned cattle are a major management concern on farms, causing significant risks for other animals and animal caretakers. Removing the horns, or disbudding, has benefits for both cattle and human safety.

The term disbudding refers to the destruction or excision of horn-producing cells before skull attachment, while dehorning involves the excision of the horn after skull attachment. Time of attachment varies, but scientific literature indicates that this occurs around 8 weeks of age.[12] Therefore, best practice is to conduct disbudding at the earliest age possible, before 8 weeks of age.

There is scientific evidence that both disbudding and dehorning are painful procedures. Administration of local anesthesia,[13,14] NSAIDs[15,16,17] and sedatives[18] all have been shown to provide benefits to calf welfare. An effective pain management protocol is required and should be implemented with veterinarian guidance.

Acceptable methods for disbudding include application of caustic paste or an electric/gas iron to destroy the horn producing cells. Caustic paste should be applied within the first few days of life and is less effective and discouraged after the calf is 2 weeks of age.

Additional management is required for caustic paste disbudding, including protecting treated calves from rain and limiting social interactions to ensure paste only affects the horn bud area. Effective pain management is still required with this method of horn removal.

Cows that have either been missed or have developed scurs should be monitored and, if deemed necessary, dehorned. Any attempt to permanently remove the horn after 8 weeks of age is considered a surgical procedure and should only be performed by a licensed veterinarian.

The use of polled genetics may be an option for farmers depending on the dairy's breed of cattle and the genetic diversity of polled genetics. Currently there are challenges in the diversity and availability of polled genetics available in the U.S. dairy herd.

✓ **Pain mitigation for disbudding is provided.**

All methods of disbudding and dehorning cause pain.[19,20] AABP recommends that pain management be considered the standard of care during all dehorning and disbudding procedures. Farmers are encouraged to work with their VOR, who is best able to develop the most appropriate, individualized pain management protocol for their operation. Scientific evidence supports that it is possible to enhance animal welfare associated with these necessary procedures with the implementation of pain management protocols.

Local Anesthesia

Use of a local anesthetic mitigates the immediate pain associated with disbudding and dehorning and provides up to five hours of post-procedural analgesia. There are a variety of local anesthetic techniques including:

- Cornual nerve block
- Horn bud infiltration

Local anesthetic protocols should be determined and prescribed by the VOR. Federal law restricts the use of local anesthetics to use by or on the order of a licensed veterinarian.

Systemic Pain Relief

NSAIDs should be used to provide additional, longer lasting pain relief. The use of injectable, topical or oral NSAIDs are acceptable for pain mitigation in the immediate post-operative period. The type of NSAID used should be prescribed by the VOR. NSAID considerations include:

- Meloxicam has been shown to mitigate post-procedure pain for up to 48 hours after a single dose of the drug.
- Topical NSAID applications make the administration of NSAID therapy at the time of disbudding or dehorning practical in most instances.
- Oral, IV or IM administration is difficult although further study is warranted to determine its effectiveness in mitigating dehorning pain.

There are currently no approved drugs in the U.S. for use in cattle with an indication to provide analgesia associated with dehorning pain. Regulations under the AMDUCA allow extra-label drug use provided a valid VCPR exists and the drug selection process, records and withholding times outlined in the AMDUCA regulations are followed.

When it comes to pain mitigation, the prescribing veterinarian must assign an adequate meat and milk withdrawal interval (WDI) in instances of in instances of extra-label drug use as prescribed by AMDUCA. The best resource for veterinarians to find an appropriate WDI is the FARAD.

Veterinarians should submit the required information (dose, route, frequency, duration, weight of animal) and FARAD will provide a WDI. Veterinarians should then save this in their records as evidence of due diligence in assigning a WDI.

Pre-Weaned Calf Management Protocol

✓ **The written herd health plan has a written protocol for pre-weaned calf care that includes language specific to areas of pre-weaned calf management.**

The written herd health plan must have a written protocol for pre-weaned calf care that includes language specific to all of the areas outlined within this chapter.

Appendix 4

08

Non-Ambulatory Animals

Appendix 4

Management Checklist

- ✓ Non-ambulatory animals are moved using proper methods, including the use of special equipment.
- ✓ Non-ambulatory animals are provided prompt medical care.
- ✓ Non-ambulatory animals are provided access to feed, water, protection from heat and cold for typical climatic conditions, isolation from other ambulatory animals and protection from predators.
- ✓ Facilities are designed to have a location to segregate weak, sick or injured animals.
- ✓ The location for weak, sick or injured animals provides animals with: feed, water, protection from heat and cold for typical climatic conditions, isolation from other ambulatory animals and protection from predators.
- ✓ The written herd health plan has a written protocol for non-ambulatory animal management that includes language specific to areas of non-ambulatory animal management.

Moving Non-Ambulatory Animals

✓ **Non-ambulatory animals are moved using proper methods including the use of special equipment.**

The prognosis of an animal should always be considered before the decision is made to move an animal. If the animal is highly unlikely to become ambulatory again, with little chance of recovery or good quality of life, the animal should be promptly euthanized in accordance with the herd health plan (See Chapter 9: Euthanasia).

Prevention, preparation and prompt action are keys to the proper handling of non-ambulatory animals.

Animals that are at high risk for becoming non-ambulatory are:

- Post-fresh animals (calcium deficiency, calving injury, etc.)
- Animals weak due to prolonged sickness or age
- Severely lame animals
- Animals emaciated due to prolonged sickness or nutritional deficiencies

Facility risk factors that may lead to non-ambulatory animals:

- Slippery floors
- Improperly designed loading areas into parlors and trucks
- High-density situations

Non-ambulatory animals that cannot be carried should be moved using an appropriate mechanism.

Appropriate mechanisms for movement include:

- Sled
- Belting with reinforced sides
- Sling
- Skidsteer bucket
  - Must be large enough to hold the entire animal
- Palleted forklift
  - Construct a pallet platform to fit over the forks
  - Angle the pallet's leading edge to form a ramp for rolling the cow onto the pallet
  - Equip the pallet with straps to prevent the animal from falling off
  - Never use exposed forks

In all situations, animals must be restrained appropriately as to not risk or cause additional injury.

Appropriate Procedure for non-ambulatory animal movement:

- Best practice is to have at least three people available to transfer an animal onto the movement mechanism.
  - One person should run the equipment being used.
  - The other two individuals should move the animal onto the selected movement device.
  - To ensure the safety of the animal, individuals should walk alongside the animal and the movement device.
- Gently roll a non-ambulatory animal onto the movement device.
  - If the animal goes down in a pen or alley, plywood or belting may be attached to a truck or tractor that can be driven slowly and carefully to a transfer point.
  - Carefully transfer the animal from the plywood or belting to an appropriate movement device as listed above. When using any of these methods, proper restraint of the animal should be utilized.

Proper Care For Non-Ambulatory Cows

PREVENT

1. Ensure cows are **consuming a balanced ration** to prevent metabolic disease and manage body condition
2. Ensure cows are able to **rise soon after calving**
3. **Observe cows daily** for any abnormal activities
4. Ensure employees are trained in low-stress cow handling and that alleyways are properly maintained to **prevent cows from slips and falls** and for proper feet and leg support

PLAN

1. Identify **who is trained** and should be called in a non-ambulatory cow situation. *The FARM Program requires annual animal care employee trainings.*
2. Have a team **trained to properly move** a non-ambulatory cow
3. Have a written non-ambulatory cow **protocol**. *The FARM Program requires written protocols for managing non-ambulatory cattle.*
4. Have an identified hospital area
5. **REMAIN CALM**

CARE

1. Provide **deep bedding** at least 6" deep — sand is best
2. Provide **safe shelter** from the elements and away from other cows
3. Put feed and water in tubs that do not tip over and are within easy reach — **check availability at least twice a day**
4. Lift the cow using **proper protocol** or roll her onto her other side twice a day
5. Consult with your herd veterinarian about a **proper treatment plan** for the cow
6. **Never drag cow**

COMMON CAUSES 5 Ms

M — MILK FEVER
Symptoms: dull/weak; trembling/ twitching; temperature below 101F; cold, droopy ears

M — TOXIC MASTITIS
Symptoms: dull/weak; temperature extremes (high or low); sunken eyes; abnormal milk; heat, pain and swelling of one or more quarters

M — TOXIC METRITIS
Symptoms: dull/weak; temperature extremes (high or low); sunken eyes; watery, colored or cloudy vaginal discharge and odor

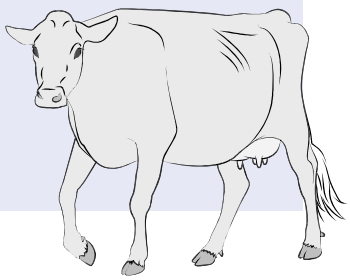
M — MUSCULOSKELETAL DAMAGE
Symptoms: abnormal angle and/or swelling to limb; suspect fracture or dislocation; paralysis

M — MASSIVE INFECTION
Symptoms: dull/depressed; sunken eyes; temperature extremes (high or low); difficulty breathing

ASSIST THE COW TO STAND IF

a physical exam and initial treatment have been completed and she:

- ✓ Is bright and alert
- ✓ Is not severely trembling or twitching
- ✓ Does not have evidence of severe disease
- ✓ Does not appear severely weak
- ✓ Appears to have normal and functioning limbs



Source: The Proper Care for Non-Ambulatory Cows poster at NationalDairyFarm.com

Non-Ambulatory Animal Movement: Sled/Belting

1

Animal Restraint

When moving a non-ambulatory animal, a halter should be correctly placed on animal's head with a high-quality lead rope. The lead rope should be tied above the hock on the same side the animal's head is turned toward. Two additional ropes should be tied: 1.) Above the knee on the opposite side of the head 2.) Above the hock on the opposite side of the head.

2

Movement Onto Transporting Device

With all three team members working together, slowly roll the animal onto the transportation device.

3

Movement to Hospital Pen

Secure the transportation device to a tractor or similar vehicle with the ability to slowly pull the transportation device with the animal safely in place. Have at least two individuals walk alongside of the animal to ensure its safety.

4

Hospital Pen

Once the animal reaches the hospital pen, gently slide it off the transportation device into a clean, well-bedded area.

Source: Dairy Care 365, Merck Animal Health

Non-Ambulatory Animal Movement: Skidsteer/Bucket Loader

1

Follow the step (left). Bring the bucket to the animal. Ensure padding is at the bucket lip edge to eliminate risk of injury by bucket. Ensure the bucket size is large enough for the animal needing to be moved.

2

Using at least two individuals, slowly slide the animal fully into the bucket.

3

The bucket operator should slowly lift the bucket while at least two individuals slowly slide the animal fully into the bucket.

4

Once the animal is secured in the bucket, At least two individuals should walk alongside of the bucket loader while it is in motion, constantly monitoring the cow.

5

Once in the hospital pen location, the bucket should be slowly lowered with at least two individuals ensuring the animal remains secure. Slowly back the bucket loader away from the animal placing it onto a clean, well-bedded area.

Improper Movement

Animals should never be dragged using mechanical force.

Animal should never be moved horizontally with hip lifts or lifted vertically where their feet cannot touch the ground.

Except for emergency cases where an animal must be moved a few feet before an appropriate movement device can be used (i.e., if a cow becomes non-ambulatory in the milking parlor and the animal is likely to recover and have a good quality of life), cattle are not to be pulled, dragged or moved horizontally or vertically by mechanical force applied directly to the animal. Hip lifts/clamps should never be used to move animals, only to lift and lower them, and the animal should never be raised with any device to where her feet cannot touch the ground.

If the animal must be dragged because no other moving alternative exists or because it can only be saved by dragging (i.e., if a cow falls into a manure pit where the likelihood of drowning is imminent), pad non-injured limbs and use padded belts to which a rope, chain or cable can be attached. Drag the animal the shortest possible distance to a point where a better method of moving can be employed. If this procedure cannot be done humanely, then the animal is to be euthanized in place and then moved.

Using an adequate number of trained people along with the appropriate equipment and handling devices will ensure the safety of the non-ambulatory animal and animal caretakers, and increase the likelihood of recovery.

Non-Ambulatory Animal Care

- ✓ **Non-ambulatory animals are provided prompt medical care.**
- ✓ **Non-ambulatory animals are provided access to feed, water, protection from heat and cold for typical climatic conditions, isolation from other ambulatory animals and protection from predators.**

When an animal becomes non-ambulatory, it should receive prompt medical care.

Non-ambulatory animals should be separated from the ambulatory animals in the herd and protected from heat, cold and predators to prevent further damage to the animal and enhance medical treatment.

A non-ambulatory animal should have access to clean water and feed. Water should be provided multiple times and brought directly to the non-ambulatory animal throughout the day and night in order to maintain hydration, especially when water in buckets may be knocked over. The diet of a non-ambulatory animal may need to be adjusted from its healthy counterparts based on its feed intake abilities and special considerations for its illness or injury. Consult with a veterinarian or nutritionist to determine a proper feed ration. The recovery of a non-ambulatory animal is enhanced through appropriate nutrition.

Sick or Injured Animals

- ✓ **Facilities are designed to have a location to segregate weak, sick or injured animals.**
- ✓ **The location for weak, sick or injured animals provides animals with: feed, water, protection from heat and cold for typical climatic conditions, isolation from other ambulatory animals and protection from predators.**

A hospital or sick pen that isolates the animal(s) from the herd is best practice. Because weak, sick or injured animals are more susceptible to discomfort than healthy animals, the pen should be equipped to maximize animal comfort. The location should provide feed and water, protection from heat, cold and predators, and isolation from ambulatory animals.

Herd Health Plan

- ✓ **The written herd health plan has a written protocol for non-ambulatory animal management that includes language specific to areas of non-ambulatory animal management.**

Even with the best care and adherence to a herd health plan, animals can become ill, requiring medical treatment. It is essential that animal caretakers are prepared to handle non-ambulatory animals and make prompt decisions to treat or euthanize. Having a written protocol for non-ambulatory animal management allows for consistency of training and helps ensure proper execution of the steps for the most desirable outcome for the animal.

Facility Considerations for Weak,

09

Euthanasia

Appendix 4

Management Checklist

- ✓ Criteria for identification of animals to be euthanized are established.
- ✓ Euthanasia techniques follow the approved methods of AABP and/or AVMA.
- ✓ Carcass disposal is conducted using the appropriate method in accordance with applicable local ordinances.
- ✓ The written herd health plan has a written protocol for euthanasia that includes language specific to areas of euthanasia.

Euthanasia is an unfortunate but necessary part of life on a dairy farm. No one wants to lose an animal or see an animal suffer.

When an animal's quality of life has decreased or when pain and suffering cannot be alleviated, euthanasia is the ethical and humane thing to do.

✓ **Criteria for identification of animals to be euthanized are established.**

Animal caretakers must be provided with guidance and continuing education or training to recognize situations where euthanasia is the best option for an animal.

If an animal becomes non-ambulatory, the animal caretaker must determine immediately whether the injured animal is otherwise healthy and can be nursed back to health or cannot be saved.

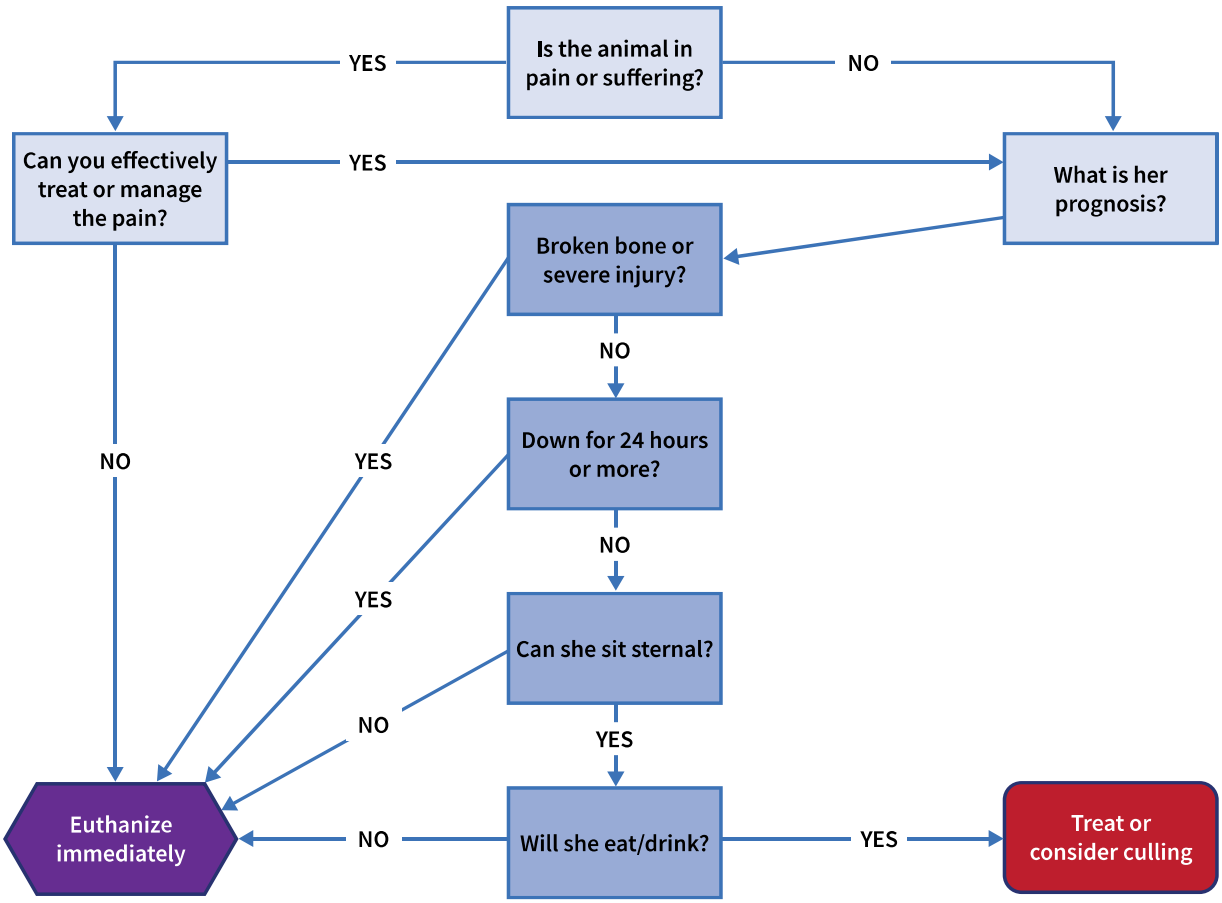
If there are indications that the non-ambulatory animal can recover, and quality of life can be re-established, dairy operations should follow their non-ambulatory animal protocol.

However, when an animal's quality of life is decreased or when pain and suffering cannot be alleviated, euthanasia is appropriate.

Below is an example of a decision tree. This tree should be customized for a farm with a veterinarian's assistance.

✓ **Euthanasia techniques follow the approved**

FIGURE 13: Euthanasia Decision Tree



Source: Adapted from Dr. Brandon Treichler, DVM

Indications for Euthanasia

The following conditions or situations[1] may lead to an animal being compromised to such an extent that euthanasia should be performed:

- Catastrophic fracture, trauma or disease of the limbs, hips or spine resulting in immobility or inability to stand
- Bleeding uncontrollably from a major blood vessel
- Inability to maintain sitting upright position with head held up (sternal recumbency)
- Inability to move and raise front legs once lifted under assistance
- Loss of quality of life. Examples may include but are not limited to:
  - Disease conditions that produce a level of pain and distress that cannot be managed adequately
  - Emaciation and/or debilitation from disease
  - Age or injury that result in an animal being too compromised to be transported or marketed
  - Disease conditions for which no effective treatment is known (e.g., Johne's disease, lymphoma)
  - Diseases that involve a significant threat to human health (i.e., rabies)
  - Chronic repeated bloating of the abomasum or rumen
  - Chronic pneumonia and difficulty breathing/gasping for air
  - Advanced ocular neoplastic conditions ("cancer eye")
  - Disease conditions for which treatment is cost prohibitive
  - Extended drug withdrawal time for clearance of tissue residue
  - Poor prognosis or prolonged expected recovery

Euthanasia Decision Making Considerations

The following criteria should be considered for the care of compromised cattle:

- Pain and distress of animal
- Likelihood of recovery
- Ability to get to feed and water
- Drug withdrawal time
- Economic considerations
- Condemnation potential
- Diagnostic information

TABLE 4: Recommended Methods for Practical Euthanasia

Method	Risk to Human Safety	Skill Required	Potential Public Perception Issues	Adjunctive Method Required
Gunshot	high	moderate*	moderate	no
Penetrating captive bolt	moderate	moderate*	some blood and motion	yes
Barbiturate overdose	low	moderate*	perceived well	no

**Operator Training Required* *Reference: Practical Euthanasia of Cattle (Animal Welfare Committee of AABP, 2013) Online at aabp.org/Resources/AABP_Guidelines/EUTHANASIA-2019.pdf*

methods of AABP and/or AVMA.

If an animal appears to be suffering from any of the indications requiring immediate euthanasia, the procedure should be performed by designated animal caretakers trained to perform euthanasia. The technique must follow the approved methods of the AABP or the AVMA. Proper euthanasia techniques include initial method, how to confirm death and a secondary method (if needed).

Approved primary methods of euthanasia recommended by AABP include:

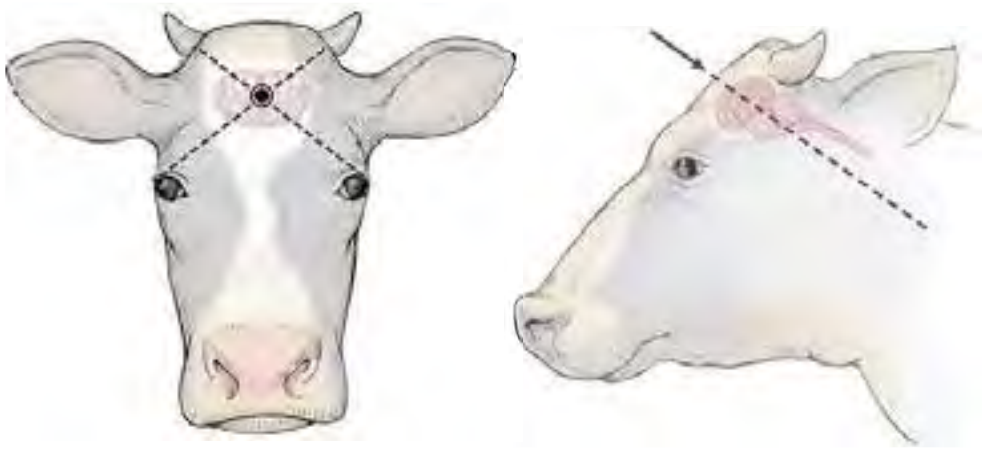
- **Gunshot:** When properly executed, gunshot induces instantaneous unconsciousness and death, is inexpensive and does not require close contact with the animal. It should be emphasized that this method should only be attempted by individuals trained in the use of firearms and who understand the potential associated dangers. Firearm options include handguns (pistols), rifles or shotguns. Current recommendations suggest that the .22 caliber handgun or rifle loaded with a solid-point bullet is sufficient for calves but may not be the best choice for consistent use on adult animals.
- **Penetrating Captive Bolt:** Captive bolt devices ("guns" or "stunners") are either penetrating or non-penetrating. Only penetrating captive bolt devices are approved for euthanasia of mature bovines and, according to AVMA Guidelines for Euthanasia of Animals, must not be used as the sole method of euthanasia. The bolt gun must be placed firmly against the skull at the same entry point previously described for a gun shot. Since use of the captive bolt gun requires close proximity to the animal, adequate restraint and prior sedation or tranquilization may be required. It is critical to maintain and clean the bolt gun as described by the manufacturer. Additionally, selection of cartridge strength may vary among manufacturers and the appropriate type and strength for the size of the animal must be used. Store cartridges in a cool dry area, away from humid environments. Exposing cartridges to moisture can affect burning of the propellant and thus lower the bolt speed and penetrating force.
- **Barbiturate Overdose:** When properly

administered by the intravenous route, barbiturate overdose results in rapid loss of consciousness and death. When using sodium pentobarbital for this purpose, an appropriate dose is typically 60-80 milligrams per kilogram. When choosing a barbiturate for euthanasia, the barbiturate selected should be potent, long acting and stable in solution. The carcass of barbiturate-treated animals is considered unfit for human or animal consumption.

Barbiturates can persist for long periods of time in the environment, which poses a risk to scavenging wildlife or companion animals. Ingestion of pentobarbital contaminated tissues by wildlife or rendered material consumed by domestic pets can induce toxicities. Finally, the use of pharmaceuticals limits carcass disposal options as renderers are less likely to accept animals euthanized by these methods.

Barbiturates are a controlled substance regulated by the Drug Enforcement Administration (DEA).
Use of barbiturates are restricted to use by or on the order of a licensed veterinarian with a valid DEA license.

NOT BETWEEN THE EYES!



Gunshot Recommendations

The AVMA Guidelines for the Euthanasia of Animals recommends the use of solid-point bullets. The 12-, 16-, and 20-gauge shotguns are a good choice for euthanasia of adult cattle. The 28 or .410-gauge shotgun is an excellent choice for use in calf euthanasia. If using a shotgun loaded with shot shells, the operator should be very conscious of the distance from the gun barrel to the animal as projectiles will spread out into a larger pattern. Ideally, to obtain maximum consistency and efficacy of euthanasia, it is desired that the BBs from the shot shell make contact with the skull as a compact mass. When using a handgun, the firearm should be held within 1-2 feet of the intended target and the bullet should be directed perpendicular to the front of the skull to minimize the likelihood of ricochet. In cattle, the point of entry of the projectile should be at the intersection of two imaginary lines, each drawn from the outside corner of the eye to the base of the opposite horn.

Source: vetmed.iastate.edu/vdpam/about/production-animal-medicine/dairy/dairy-extension/humane-euthanasia/euthanasia-downloads

Determination of Unconsciousness

A state of unconsciousness must be established immediately following the initial euthanasia procedure. It is critically important to confirm unconsciousness and then confirm death.

Secondary or adjunctive euthanasia methods must not be used until the animal has been determined to be unconscious. Signs may include:

- Absence of corneal reflex
- Absence of vocalization
- Absence of gag reflex
- Lack of rhythmic respiration
- No coordinated attempt to rise or right itself

Confirmation of Death

Confirmation of death is necessary regardless of what method of euthanasia is chosen. The primary indicator for death is cardiac arrest. Lack of a heartbeat and respiration for 3-5 minutes should be used to confirm death. Using a stethoscope placed behind the left elbow is the best method to confirm cardiac arrest. If the animal is unconscious but death cannot be confirmed, a secondary method of euthanasia must be immediately employed.

Examples of a secondary method include:

- Exsanguination (cutting the jugular veins and carotid artery in the neck or aorta rectally)
- Pithing (inserting a rod into the brain stem to cause destruction)
- Administration of a saturated salt such as potassium chloride, magnesium chloride or magnesium sulfate
- A second shot

It is inappropriate and inhumane to exsanguinate, pith or administer a saturated salt solution to an animal that is conscious. A second shot should be immediately administered to an animal that is not rendered unconscious from the first gunshot or captive bolt.

✓ **Carcass disposal is conducted using the appropriate method in accordance with applicable local ordinances.**

Dead animals, either euthanized or expired from natural causes, are potential sources of infection. Their carcasses must be promptly disposed of using appropriate methods, which may include rendering, burial, composting or incineration in accordance with applicable local ordinances. Consultation with local ordinances and the state veterinarian should be conducted to determine the appropriate method of disposal.

Dead animals should quickly be moved to a designated location away from healthy animals and away from public view. Where warranted and feasible, waste and bedding of an animal that has died should be removed from the facility to an area inaccessible to other animals.

A postmortem examination on well-preserved animals can provide important animal health information and prevent further losses to the herd.

✓ **The written herd health plan as a written protocol for euthanasia that includes language specific to areas of euthanasia.**

A written herd health plan that includes a protocol for euthanasia helps ensure that the decision to euthanize an animal can be made in order to reduce any unnecessary pain and suffering. Additionally, a protocol also allows for those animal caretakers to be trained to conduct euthanasia according to AABP/AVMA guidelines, allowing for a humane death.

Appendix 4

10

Fitness to Transport

Appendix 4

Management Checklist

✓ The facility has an effective written protocol for fitness to transport that includes the definition of animals that are eligible to be marketed and outlines adherence to milk and meat withdrawal times.

Dairy animals are an important source of beef in the U.S. Approximately 20% of the nation's total beef production on an annual basis comes from the dairy sector, including fed dairy cattle and marketed cows and bulls. This chapter specifically focuses on considerations for the marketing of dairy animals for beef production. For information on animal care for beef animals (including dairy steers), follow the guidelines of the Beef Quality Assurance (BQA) program.

Dairy Beef

Marketing a dairy animal as beef is an important part of dairy farming. A dairy farmer must ensure the appropriateness of transitioning a dairy animal to the beef sector. In best practice, an animal should NOT be marketed if:

- It is non-ambulatory
- There is a reasonable chance it will become non-ambulatory at any time from leaving the farm to the slaughter facility
- It does not meet the food safety requirements for withdrawal periods or disease
- It is in poor body condition (less than BCS 2)
- It has not met all treatment withdrawal times for milk and meat
- Calving is imminent and likely to occur during the transportation or marketing process
- It has bone fractures of the limbs or injuries to the spine
- It has a condition that will not pass pre-slaughter inspection at a packing or processing facility.
  - If unsure, consult with your veterinarian before transporting an animal to a packing or processing facility.

USDA inspectors are instructed to look for animals that present a possible risk to the food supply. They're also trained to look for signs of disease or recent animal health product administration to determine if an animal should be subjected to additional testing and possible removal from the food chain. In best practice, the dairy retains treatment records for at least two years.

Dairy farmers should not transport animals with conditions that are unlikely to pass pre-slaughter inspection.

These conditions include, but are not limited to:

- Cancer eye, blindness in both eyes
- Drug residues
- Fever greater than 103° F
- Peritonitis
- Cows that are calving or have a high likelihood of calving during transport
- Fractures or lameness (3 or greater on the FARM locomotion scale)
- Distended udders causing pain and ambulatory issues
- Unreduced prolapses
- Visible open wounds
- Suspected central nervous system symptoms

Conditions that Warrant Additional Testing at USDA Slaughter Facilities

The following list contains descriptions, directly from USDA documents, of conditions that may warrant testing of carcasses for drug residues:

- Mastitis
- Metritis
- Peritonitis and surgery
- Injection sites
- Other disease symptoms
- Signs of treatment

Additional considerations that should be followed to ensure a safe beef supply:

- The facility maintains permanent (written or electronic) treatment records, available for review by the VOR, for the treatment of the facility's common diseases that include:
  - Date of treatment
  - Animal treated identification
  - Name of the treatment used
  - Disease/condition being treated
  - Dosage administered
  - Route of administration
  - Duration of the treatment
  - Specified withdrawal times for milk and meat to ensure food safety
- The herd health plan includes written protocols for the treatment of common diseases including:
  - Mastitis
  - Metritis
  - Milk fever
  - Ketosis
  - Displaced abomasum (DA)
  - Pneumonia
  - Diarrhea
  - Any other routinely occurring diseases identified by the veterinarian
- The facility has a written protocol for fitness to transport that includes the definition of animals that are eligible to be marketed and outlines adherence to milk and meat withdrawal times.
- All family and non-family employees who determine fitness to transport have documented annual continuing education on the written fitness to transport protocol.
- Each animal is permanently identified.
- All meat tissues from animals processed for meat production have tested negative for violative residues in the last three years.

Transportation

Transporters play a critical role in the health and welfare of dairy cattle. Proper handling and transport can reduce sickness and injury, prevent bruises and improve the quality of meat from these animals. In best practice, animal transporters are trained in how to properly move cattle up and onto the trailer, distribute cattle correctly on the trailer, employ hauling techniques that reduce cattle stress and handle emergency situations. For additional resources related to transportation best practices, please refer to the BQA transportation modules.

Dairy farmers are encouraged to have transporters sign a cow care agreement indicating that they have received basic stockmanship training and agree to treat all animals humanely. Using a transportation company that is knowledgeable about your animal care expectations provides safety and comfort of the animals during transport.

Loading and Unloading

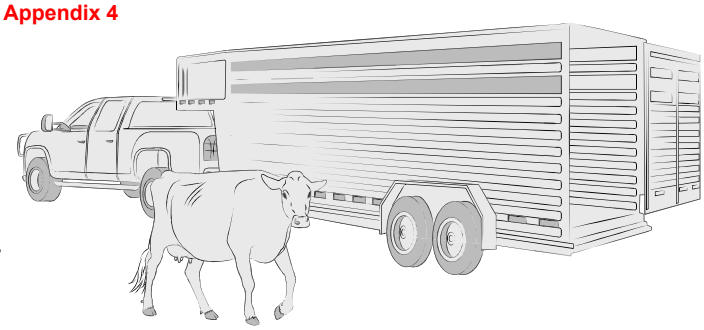
Under best practice, animals are loaded and unloaded for transit in a manner that minimizes stress. The process of being moved, especially if it involves a loading chute, is a potentially stressful experience to many animals. Three measures should be taken to minimize stress:

1. Train animal caretakers in proper loading and unloading practices
2. Properly locate and design loading areas
3. Minimize the number of directional changes an animal must take.[1]

Prods, canes and other cattle handling aids are only used as a last resort, in emergency situations, and not in routine animal handling.

Animal caretakers should observe proper loading densities and plan to load or unload animals at the time of day that is best for moving the animals. In best practice, sufficient labor and appropriate equipment and/or facilities (i.e., ramps) are available for loading or unloading animals.

Considerations When Transporting Dairy Animals



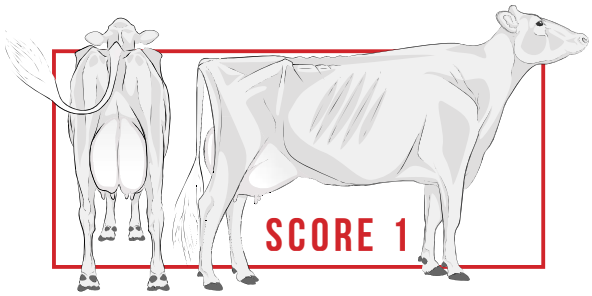
Make decisions in a timely and efficient manner, always considering animal well-being first.

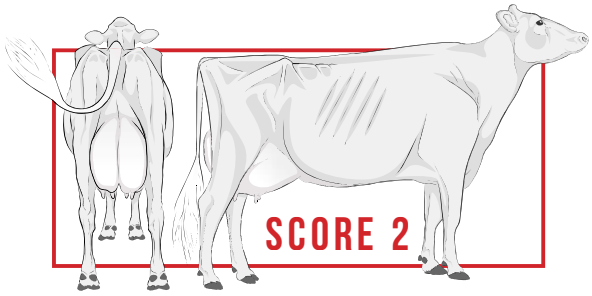
DO:

- Treat, cull or euthanize animals promptly. Segregate sick, injured and non-ambulatory animals from the rest of the herd.
- Use a BQA Transportation (BQAT)-certified company that is knowledgeable about your animal care expectations and provides safe and comfortable transport for animals. To become certified visit: www.bqa.org.
- Delay transport of animals that appear exhausted or dehydrated. Cows experiencing heat stress or exhaustion may exhibit open-mouth panting and be reluctant to move. Transport once the animal is rested, fed and rehydrated.
- Milk lactating cows just prior to transport.

DON'T TRANSPORT ANIMALS:

- That are non-ambulatory.
- Until all proper milk and meat withdrawal times have been followed. Refer to the ***FARM Milk & Dairy Beef Residue Prevention Manual*** for proper withdrawal times.
- With bone fractures of the limbs or injuries to the spine.
- Animals with recent fractures unrelated to mobility should be culled and transported directly to a packing or processing facility.
- In poor body condition, generally a body condition score of less than 2:





- With conditions that risk their well-being and are unlikely to pass pre-slaughter inspection, including but not limited to:
  - Emaciated animals
  - Cancer eye
  - Blindness in both eyes
  - Fever greater than 103°F
  - Drug residues
  - Peritonitis
  - Visible open wounds
  - Suspected central nervous system symptoms
  - Fractures or lameness *(a score greater than 2 using the FARM locomotion scoring system)*
  - Unreduced prolapses
  - Cows that are calving or have a high likelihood of calving during transport
  - Distended udder causing pain and ambulatory issues

Always consult with your veterinarian if you are unsure if an animal should be transported. And, remember, abuse is never tolerated – including pre-transport and during transport.

Download the transport poster in the FARM Resource Library

Trucks and Trailers

Trucks and trailers have an impact on animal care. Even though transport vehicles are not stationary, they are facilities that require the same consideration for cow comfort and needs, including:

1. A clean/disinfected truck or trailer when moving young stock or cull cows
2. Sides high enough to prevent animals from jumping over them
3. Non-slip flooring that provides secure footing (avoid abrasive floor and wall surfaces)
4. Ventilation and proper bedding to protect animals from weather extremes
5. Adequate vehicle covering to protect animals from adverse weather

In-Transit Care

Proper in-transit care will minimize animal injuries, bruises and carcass damage, which can impair an animal's well-being and value. Transport crews should be knowledgeable about animal care expectations and skilled in handling animals properly. In general, chances for injuries decrease when animals on a truck are confined in several smaller groups. Weak or unhealthy animals are only shipped to a veterinarian (not to a processing facility) and segregated from healthy cows during loading and transit. Additional care should be provided to weak or unhealthy cows during transport.

An adequate amount of time for the trip should be allotted to include periodic checking of the animals' condition. Drivers should start and stop the vehicle smoothly and slow down for curves and corners. If an animal falls in transit, it should be helped to its feet, provided it does not pose a risk to the handler, and possibly segregated from the other animals for the rest of the trip. Provisions for water should be made immediately upon arrival at the destination and provisions for feed should be made if the trip takes more than 24 hours. Feeding high-fiber dry feed for 48-72 hours before shipping reduces the moisture content of manure and improves air quality, animal comfort and hygiene.

All workers and handlers should be properly trained in handling dairy animals and have a basic understanding of typical dairy cattle behavior. All state and national regulations regarding transportation should be followed.

11

Appendix, Glossary and References

Appendix A: Governance Chart

Appendix B: Animal Observation Scoring

Appendix C: Willful Mistreatment or Neglect Protocol Overview

Appendix D: Training Resource Library & Website

Glossary

References

Appendix A: Governance Chart

FARM Animal Care Guidelines

The National Dairy FARM Animal Care Program standards are formally revised every three years through a strenuous, year-long process.

Who Drafts and Approves FARM Animal Care Program Guidelines?

NMPF Animal Care Technical Writing Group

Nate Chittenden*, Agri-Mark, Inc.
Nigel Cook, BVSc, University of Wisconsin-Madison
David Darr, Dairy Farmers of America
Chase Decoite, National Cattlemen's Beef Association
Richard Doak, DVM, Mid-Maryland Dairy Veterinarians
Marcia Endres, PhD, University of Minnesota
Fred Gingrich, DVM, American Association of Bovine Practitioners
Paul Humphrey, Foremost Farms USA
Karen Jordan*, DVM, Dairy Farmers of America
Steve Maddox*, California Dairies, Inc.
Antone Mickleson, Northwest Dairy Association/Darigold
Tim Raasch, Land O' Lakes
Kris Scheider*, Foremost Farms USA
Brandon Treichler, DVM, Select Milk Producers, Inc.
Cass Tucker, University of California, Davis

NMPF Animal Health & Well-Being Committee

Mike Barnes*, Agri-Mark, Inc.
Doug Chapin*, Michigan Milk Producers Association
David Darr, Dairy Farmers of America
Dan deGroot*, Northwest Dairy Association/Darigold
Garrett DeVries*, Dairy Farmers of America
Zack Dombek, DVM, Land O' Lakes
Rodney Ervin, Lone Star Milk Producers
Stephen Ford, Southeast Milk, Inc.
Alan Gerratt*, Dairy Farmers of America
Fred Gingrich, DVM, American Association of Bovine Practitioners
Walt Guterbock*, DVM, Select Milk Producers, Inc.
Jerrel Heatwole*, Dairy Farmers of America
Karen Jordan*, DVM, Dairy Farmers of America
Henry Kamagy, DVM, Upstate Niagara Cooperative, Inc.
Kelly King*, FarmFirst Dairy Cooperative
Kate Lott, DVM, Tillamook County Creamery
Josh Luth, Foremost Farms USA
Antone Mickleson, Northwest Dairy Association/Darigold
Randy Mooney*, Dairy Farmers of America
Mike Myatt, Cooperative Milk Producers Association
Chuck Nelson, First District Association
Mike O'Brien, Foremost Farms USA
Kevin Olson, Prairie Farms Dairy, Inc.
Dawn Raymond, First District Association
Lindsay Reames, Maryland & Virginia Milk Producers Cooperative Assn, Inc.
Patti Schaefer, First District Association
Dan Senestraro*, DVM, Dairy Farmers of America
Tom Thompson*, United Dairymen of Arizona
Kim Torrey, Upstate Niagara Cooperative, Inc.
Brandon Treichler, DVM, Select Milk Producers, Inc.
Bill Wavrin*, DVM, Northwest Dairy Association/Darigold
Leon Weaver*, DVM, Select Milk Producers, Inc.

Innovation Center Animal Care Committee

Rob Byrne, Schreiber Foods
Dave Carlin, International Dairy Foods Association
David Darr, Dairy Farmers of America
Brian Esplin*, Dairy Farmers of America
Gary Germaine, Leprino Foods Company
Marilyn Hershey*, Dairy Management, Inc.
James Jacquier*, Agri-Mark, Inc.
Jack Jeffers, Dean Foods
Michael John, Maryland & Virginia Milk Producers Cooperative Assn, Inc.
Josh Luth, Foremost Farms USA
Steve Maddox*, California Dairies, Inc.
Randy Mooney*, Dairy Farmers of America
Stan Ryan, Northwest Dairy Association/Darigold

NMPF Board of Directors

Brad Anderson, California Dairies, Inc.
Jim Baird, Lone Star Milk Producers
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Leon Berthiaume, St. Albans Cooperative Creamery
Jay Bryant, Maryland & Virginia Milk Producers Cooperative Association, Inc.
Michael Doyle, Foremost Farms USA
Craig Edler*, Dairy Farmers of America
Beth Ford, Land O' Lakes
Tony Graves*, Prairie Farms Dairy, Inc.
Brian Hardy*, Dairy Farmers of America
Jerrel Heatwole*, Dairy Farmers of America
Kent Herman*, Dairy Farmers of America
Neil Hoff*, Dairy Farmers of America
Allan Huttema*, Northwest Dairy Association/Darigold
Cornell Kasbergen*, Land O' Lakes
Jimmy Kerr, Cooperative Milk Producers Association
Jackie Klippenstein, Dairy Farmers of America
Chris Kraft*, Dairy Farmers of America
Gerben Leyendekker*, California Dairies, Inc.
Jeff Lyon, FarmFirst Dairy Cooperative
Mike McCloskey*, DVM, Select Milk Producers, Inc.
Sheryl Meshke, AMPI
Scot Meyer, Ellsworth Cooperative Creamery
Andrei Mikhalevsky, California Dairies, Inc.
Randy Mooney*, Dairy Farmers of America
Keith Murfield, United Dairymen of Arizona
Ken Nobis*, Michigan Milk Producers Association
Brad Nosbush*, First District Association
Doug Nuttleman*, Dairy Farmers of America
Tom Pittman, Premier Milk, Inc.
Leroy Plagerman*, Northwest Dairy Association/Darigold
Neal Rae*, Agri-Mark, Inc.
Jeff Raney*, Dairy Farmers of America
Levi Ransom*, Land O' Lakes
Brian Rexing*, Dairy Farmers of America
Dennis Rodenbaugh*, Dairy Farmers of America
Stan Ryan, Northwest Dairy Association/Darigold
David Scheevel*, Foremost Farms USA
Steve Schlangen*, AMPI
Nic Schoenberger*, Land O' Lakes
Dan Senestraro*, DVM, Dairy Farmers of America
Rick Smith, Dairy Farmers of America
Dennis Tonak, Midwest Dairymen's Company
Case van Steyn*, Dairy Farmers of America
Rob Vandenheuvel, California Dairies, Inc.
Jonathan Vander Dussen*, Select Milk Producers, Inc.
Simon Vander Woude*, California Dairies, Inc.
Mike Visser *, Select Milk Producers, Inc.
Larry Webster, Upstate Niagara Cooperative, Inc.
Greg Wickham, Dairy Farmers of America
John Wilson, Dairy Farmers of America
Joe Wright*, Southeast Milk, Inc.

Note that this is as of June 2019

** Committee member is also a farmer*

Appendix B: Animal Observation Scoring

Animal Observations Summary

OBSERVATION SUMMARY					
	LACTATING COWS	PRE-WEANED CALVES *(heifers, bulls, steers)*	POST-WEANED HEIFERS	PRE-FRESH COWS/ HEIFERS/ DRY COWS	HOSPITAL PEN
SIGNS OF NEGLECT	✓	✓	✓	✓	✓
HYGIENE	✓	✓ *(3 days of age and older)*	✓	✓	
BODY CONDITION SCORE	✓	✓ *(3 days of age and older)*	✓		
LOCOMOTION	✓				
HOCKS	✓				
KNEES	✓				
BROKEN TAILS	✓				

Signs of Neglect

Observe all age classes

HOW	Walkthrough of the facility *(not assessing all animals at the individual level)*
WHAT TO RECORD	• Non-ambulatory cattle, including protection from ambulatory animals* • Emaciated cattle* • Severe lameness* • Catastrophic injury* • Water provision • Food provision • Protection from heat and cold provision **Record random sample of animal ID and check if they are receiving treatment*
IDEAL EVALUATOR LOCATION DURING OBSERVATION	Some measures may require being inside the pen

PRE-WEANED CALVES

Observations:

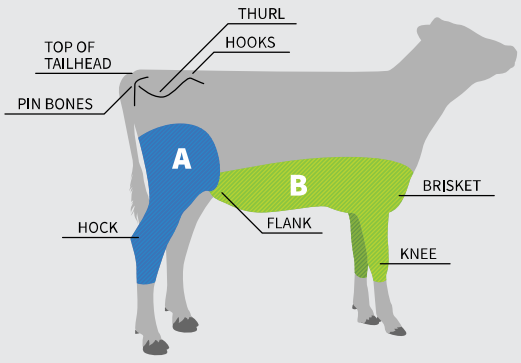
- ✓ Hygiene
- ✓ Body condition scores
- ✓ Signs of neglect (pg. 96)

IDEAL OBSERVATION TIME	During milk feeding time, otherwise it is difficult to see all relevant body parts	
IDEAL EVALUATION LOCATION DURING OBSERVATION	Outside calf hutch or pen	
WHICH CALVES TO OBSERVE	**LESS THAN 100 ON SITE** Observe all	**MORE THAN 100 ON SITE** Observe 100. Divide evenly across age groups from birth to weaning. Score first animals seen.
DO NOT OBSERVE CALVES DAY 0-2 EXCEPT FOR SIGNS OF NEGLECT		

Hygiene Scoring

PRE-WEANED CALVES

SCORE 1: CLEAN	SCORE 2: MODERATE	SCORE 3: VERY DIRTY
Mud or manure does not exceed 5.5 inches in length in areas A or B	Mud or manure exceeds 5.5 inches in length in a **single** area of A or B	Mud or manure exceeds 5.5 inches in length in **both** areas A and B



Notes:

- If both sides of animal are visible, score the worst side
- You could use an 8.5" x 11" paper to and fold the sheet of paper in half to gauge the 5.5" for calves
- Do not count feed and dust
- Look for a continuous patch or nearly continuous patch in order for it to count; do not aggregate or sum smaller, disconnected, demarcated patches
- Mud and manure can be wet or dry, moisture does not matter
- Do not count discolored hair with clean texture that would not be visible on a black animal
- Evaluator stands in an upright position, with a view of the side of the animal; do not bend over to see the underside of the belly

Body Condition Scoring

Focus on Scores 1-3 for Calves

SCORE 1

Gaunt, emaciated animal, having little to no fatty tissue around tailhead and short rib region. Extremely pronounced back, hooks and pins.

SCORE 2

Thin animal, with minimal coverage around the tailhead and short rib region. Minimal coverage over back, hooks and pins.

SCORE 3

Good conditioned animal with coverage around the tailhead and short rib region. Back, hooks and pins are not pronounced.

POST-WEANED HEIFERS

Observations:

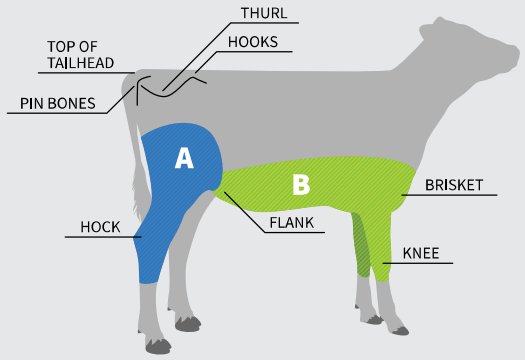
- ✓ Hygiene
- ✓ Body condition scores
- ✓ Signs of neglect (pg. 96)

IDEAL OBSERVATION TIME	Lockup time, if it occurs or is arranged	
IDEAL EVALUATION LOCATION DURING OBSERVATION	Where vision is not obstructed	
WHICH HEIFERS TO OBSERVE	**LESS THAN 100 ON SITE** Observe all	**MORE THAN 100 ON SITE** Observe 50 from oldest to youngest group(s); from as few pens as possible

Hygiene Scoring

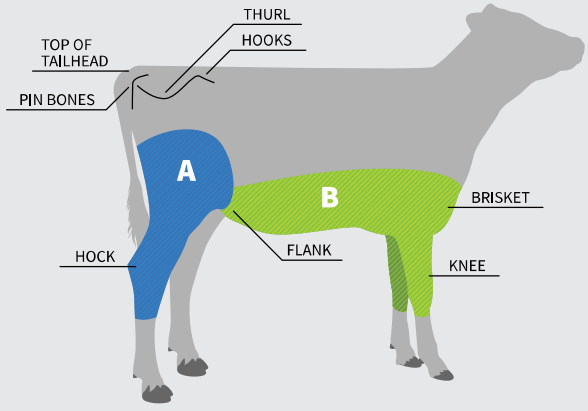
SMALL HEIFERS

SCORE 1: CLEAN	SCORE 2: MODERATE	SCORE 3: VERY DIRTY
Mud or manure does not exceed 5.5 inches in length in areas A or B	Mud or manure exceeds 5.5 inches in length in a **single** area of A or B	Mud or manure exceeds 5.5 inches in length in **both** areas A and B



LARGE HEIFERS

SCORE 1: CLEAN	SCORE 2: MODERATE	SCORE 3: VERY DIRTY
Mud or manure does not exceed 11 inches in length in areas A or B	Mud or manure exceeds 11 inches in length in a **single** area of A or B	Mud or manure exceeds 11 inches in length in **both** areas A and B



Notes:

- If both sides of animal are visible, score the worst side
- You could use an 8.5" x 11" paper to gauge the 11" in large heifers and fold the sheet of paper in half to gauge the 5.5" for small heifers
- Do not count feed and dust
- Look for a continuous patch or nearly continuous patch in order for it to count; do not aggregate or sum smaller, disconnected, demarcated patches
- Mud and manure can be wet or dry, moisture does not matter
- Do not count discolored hair with clean texture that would not be visible on a black animal
- Evaluator stands in an upright position, with a view of the side of the animal; do not bend over to see the underside of the belly

Body Condition Scoring

SCORE 1

Gaunt, emaciated animal, having little to no fatty tissue around tailhead and short rib region. Extremely pronounced back, hooks and pins.

SCORE 2

Thin animal, with minimal coverage around the tailhead and short rib region. Minimal coverage over back, hooks and pins.

SCORE 3

Good conditioned animal with coverage around the tailhead and short rib region. Back, hooks and pins are not pronounced.

SCORE 4

Slightly over-conditioned animal with more than average coverage around tailhead and short rib region, short ribs cannot be felt or seen. Back, hooks and pins have more than average coverage and bone structure difficult to see due to amount of coverage.

SCORE 5

Over-conditioned animal with thick coverage around tailhead and short rib region; short ribs cannot be felt or seen at all. Back, hooks and pins have significant coverage and unable to see bone structure to amount of coverage.

PRE-FRESH COWS & HEIFERS/DRY COWS

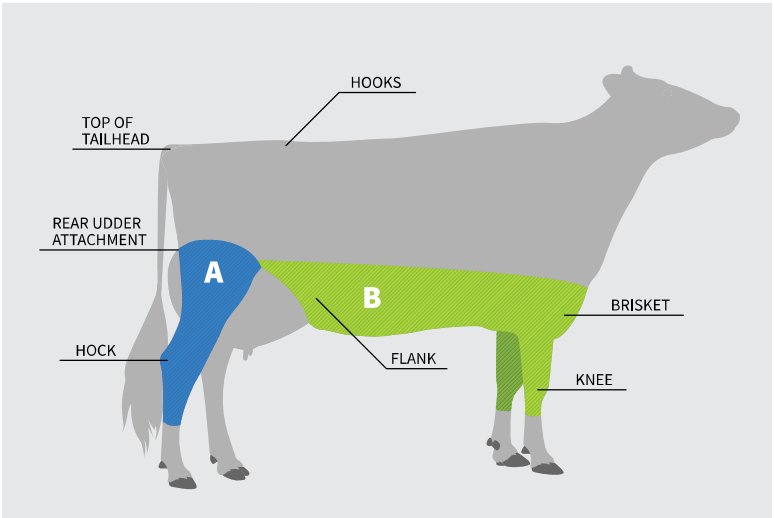
Observations:

- ✓ Hygiene
- ✓ Signs of neglect (pg. 96)

IDEAL OBSERVATION TIME	Lockup time, if it occurs or is arranged	
IDEAL EVALUATION LOCATION DURING OBSERVATION	Where vision is not obstructed	
WHICH ANIMALS TO OBSERVE	LESS THAN 100 ON SITE Observe all	MORE THAN 100 ON SITE Observe 100 from as few pens as possible

Hygiene Scoring

PRE-FRESH COWS & HEIFERS/DRY COWS		
SCORE 1: CLEAN	SCORE 2: MODERATE	SCORE 3: VERY DIRTY
Mud or manure does not exceed 11 inches in length in areas A or B	Mud or manure exceeds 11 inches in length in a **single** area of A or B	Mud or manure exceeds 11 inches in length in **both** areas A and B



Notes:

- If both sides of animal are visible, score the worst side
- You could use an 8.5" x 11" paper to gauge the 11" in pre-fresh cows and heifers/dry cows
- Do not count feed and dust
- Look for a continuous patch or nearly continuous patch in order for it to count; do not aggregate or sum smaller, disconnected, demarcated patches
- Mud and manure can be wet or dry, moisture does not matter
- Do not count discolored hair with clean texture that would not be visible on a black animal
- Evaluator stands in an upright position, with a view of the side of the animal; do not bend over to see the underside of the belly

LACTATING COWS

Observations:

- ✓ Hygiene
- ✓ Body condition scores
- ✓ Locomotion
- ✓ Hocks
- ✓ Knees
- ✓ Broken tails
- ✓ Signs of neglect (pg. 96)

Body Condition, Hygiene, Broken Tails and Knee Observation

IDEAL OBSERVATION TIME	Lockup time	
IDEAL EVALUATION LOCATION DURING OBSERVATION	In pens	
WHICH LACTATING COWS TO OBSERVE	**LESS THAN 100 ON SITE** Observe all	**MORE THAN 100 ON SITE** Observe entire pen or at least 100 from as few pens as possible

Hock Observation

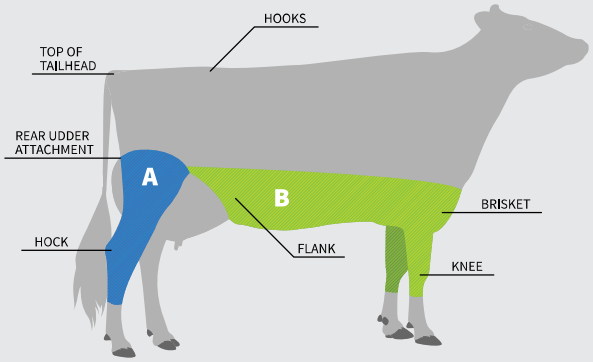
IDEAL OBSERVATION TIME	Milking time	
IDEAL EVALUATION LOCATION DURING OBSERVATION	In parlor behind cows	
WHICH LACTATING COWS TO OBSERVE	**LESS THAN 100 ON SITE** Observe all	**MORE THAN 100 ON SITE** Observe entire pen or at least 100 from as few pens as possible

Locomotion Observation

IDEAL OBSERVATION TIME	Walking back from the milking facility	
IDEAL EVALUATION LOCATION DURING OBSERVATION	Outside the exit lane, flat surface, hooves visible, do not disrupt the cows, being able to view four strides is ideal	
WHICH LACTATING COWS TO OBSERVE	**LESS THAN 100 ON SITE** Observe all	**MORE THAN 100 ON SITE** Observe entire pen (oldest and highest producing) or last 100 while walking; otherwise 100 from as few pens as possible
TIESTALL LACTATING COWS	• Ideal when cows are untied • If tied, cows must be standing, focus on score 3 animals	

Hygiene Scoring

LACTATING COWS		
SCORE 1: CLEAN	**SCORE 2: MODERATE**	**SCORE 3: VERY DIRTY**
Mud or manure does not exceed 11 inches in length in areas A or B	Mud or manure exceeds 11 inches in length in a **single** area of A or B	Mud or manure exceeds 11 inches in length in **both** areas A and B



Notes:

- If both sides of animal are visible, score the worst side
- You could use an 8.5" x 11" paper to gauge the 11" in lactating cows
- Do not count feed and dust
- Look for a continuous patch or nearly continuous patch in order for it to count; do not aggregate or sum smaller, disconnected, demarcated patches
- Mud and manure can be wet or dry, moisture does not matter
- Do not count discolored hair with clean texture that would not be visible on a black animal
- Evaluator stands in an upright position, with a view of the side of the animal; do not bend over to see the underside of the belly

Locomotion Scoring

SCORE 1
NORMAL
Animal walks easily with no gait or only minor changes. Steps may be slightly uneven.

SCORE 2
MODERATE
Asymmetric gait. Exhibits any of the following: shortening of the stride, slight limp, weight transfer while moving, but may bear weight evenly while standing.

SCORE 3
SEVERE
Difficulty bearing weight on a limb and may also exhibit obvious back arch or head bob. Animals in this category may be unable to move or be extremely reluctant to move even when encouraged by a handler.

Notes:

- Hooves must be visible while scoring, if not, then may only be able to score 3s
- If in tiestalls, only score 3s and make a note of this
- Visit FARM database library for locomotion scoring videos

Body Condition Scoring

SCORE 1

Gaunt, emaciated animal, having little to no fatty tissue around tailhead and short rib region. Extremely pronounced back, hooks and pins.

SCORE 2

Thin animal, with minimal coverage around the tailhead and short rib region. Minimal coverage over back, hooks and pins.

SCORE 3

Good conditioned animal with coverage around the tailhead and short rib region. Back, hooks and pins are not pronounced.

SCORE 4

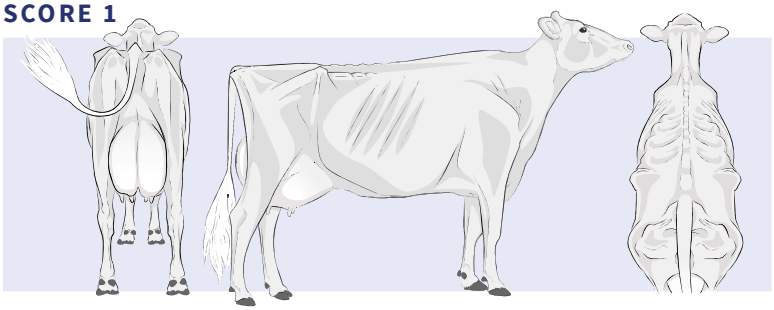
Slightly over-conditioned animal with more than average coverage around tailhead and short rib region, short ribs cannot be felt or seen. Back, hooks and pins have more than average coverage and bone structure difficult to see due to amount of coverage.

SCORE 5

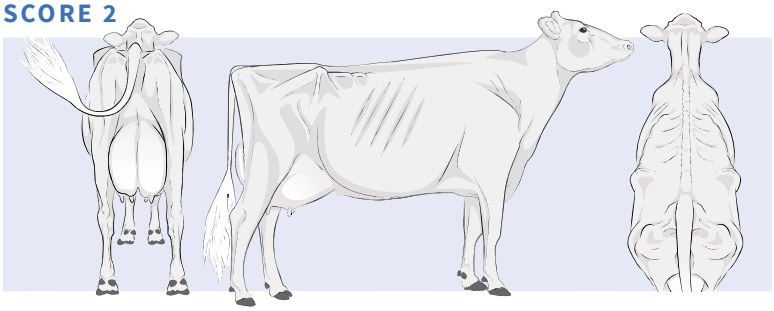
Over-conditioned animal with thick coverage around tailhead and short rib region, short ribs cannot be felt or seen at all. Back, hooks and pins have significant coverage and unable to see bone structure to amount of coverage.

Body Condition Scoring

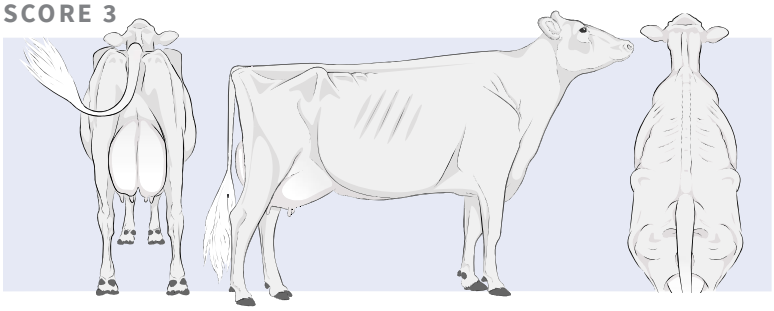
SCORE 1



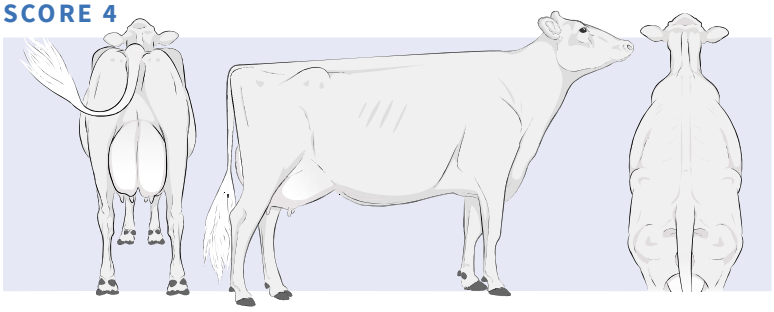
SCORE 2



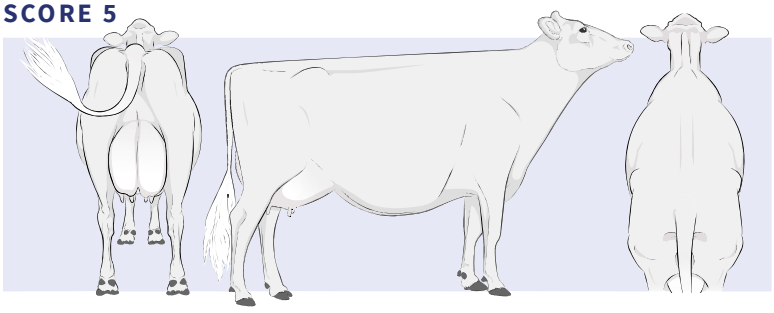
SCORE 3



SCORE 4



SCORE 5

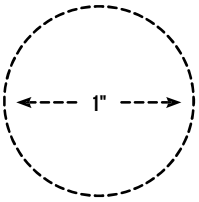


Knee Scoring

SCORE 1: NORMAL	SCORE 2: MODERATE	SCORE 3: SEVERE
Complete hair loss is less than the size of quarter (1" or 2.5 cm in length or width)	Complete hair loss is greater than or equal to the size of quarter (1" or 2.5 cm in length or width), or a dried scab or moderate swelling less than or equal to a quarter in height (1" or 2.5 cm)	Swelling greater than a quarter in height (1" or 2.5 cm)
		

Notes:

- If both sides are visible, score the worst side
- Area of hair loss must be completely bald, no hair inside
- Size of hair loss can be evaluated by length or width, it does not need to be round
- Score size of swelling by looking at deviation from the line of the leg, either from the side or from head on
- If front of knee is not visible, score only 1 or 3, based on what can be seen and make a note



A quarter can be used as an approximate 1" measurement.

Hock Scoring

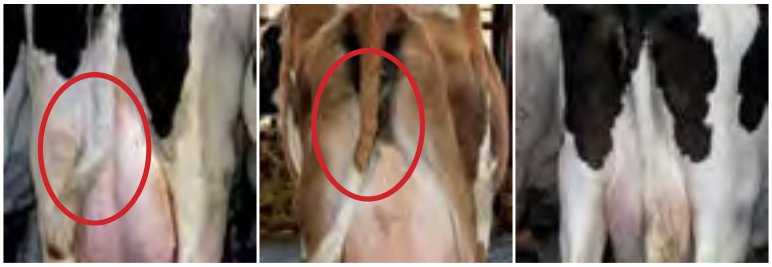
SCORE 1: NORMAL	SCORE 2: MODERATE	SCORE 3: SEVERE
Complete hair loss is less than the size of quarter (1" or 2.5 cm in length or width)	Complete hair loss is greater than or equal to the size of quarter (1" or 2.5 cm in length or width), or a dried scab or moderate swelling less than or equal to a quarter in height (1" or 2.5 cm)	Swelling greater than a quarter in height (1" or 2.5 cm)
		

Notes:

- Evaluate both the inside and outside of each hock, if visible
- If both left and right legs are visible, score the worst side
- Area of hair loss must be completely bald, no hair inside
- If there are several areas of hair loss on a hock, apply the size rules to each area,do not sum them
- Size of hair loss can be evaluated by length or width, it does not need be round
- Score size of swelling by looking at deviation from the line of the leg, either from the side or from behind

Broken Tail Scoring

BROKEN	NOT BROKEN
Tail has ANY swellings, deviations in vertebrae that can be seen, or any evidence of necrotic tissue in the tail.	Tail does not have ANY swellings, deviations in vertebrae that can be seen, nor any evidence of necrotic tissue in the tail.



Notes

- If the tail is docked, score the portion of the tail that is present
- Any form of necrotic tissue counts, regardless of reason (e.g. manure build up on tail causing self docking)
- Need to be able to see the tail in order to score this from behind the cow

Appendix C: Willful Mistreatment or Neglect Protocol

The FARM program takes all allegations of willful mistreatment or neglect of animals seriously. FARM has established this protocol to investigate credible allegations to determine if substantial evidence supports neglect or willful mistreatment of animals.

This protocol also establishes procedures, including successful implementation of an animal care improvement plan, that are required to reinstate the facility into good standing in FARM in the case of a non-egregious act of neglect or willful mistreatment.

The focus of this process is to ensure a facility's practices are consistent with FARM's standards.

Neglect is defined as a failure to carry out or perform essential management practices that ensure sound animal care. Willful mistreatment is defined as a violation, resulting in a conviction of state or local ordinance related to animal care or inflicting unnecessary and/or malicious pain, suffering or injury. Multiple incidents that establish a pattern of neglect or willful mistreatment, shall be considered egregious conduct.

Initiation of Protocol

The FARM Program will initiate the protocol when:

- Credible allegations of willful mistreatment or neglect are reported to FARM
- Credible evidence of willful mistreatment or neglect is presented or reported to FARM
  - If video is evidence provided, a third-party review of the video will be conducted
- Willful mistreatment or neglect is observed by any participant representative

Credibility of the allegation, evidence or observation will be determined by FARM in consultation with an ad hoc internal review panel. Allegations, evidence or observations determined to be misrepresented for apparent disparagement of the dairy industry will not be considered credible.

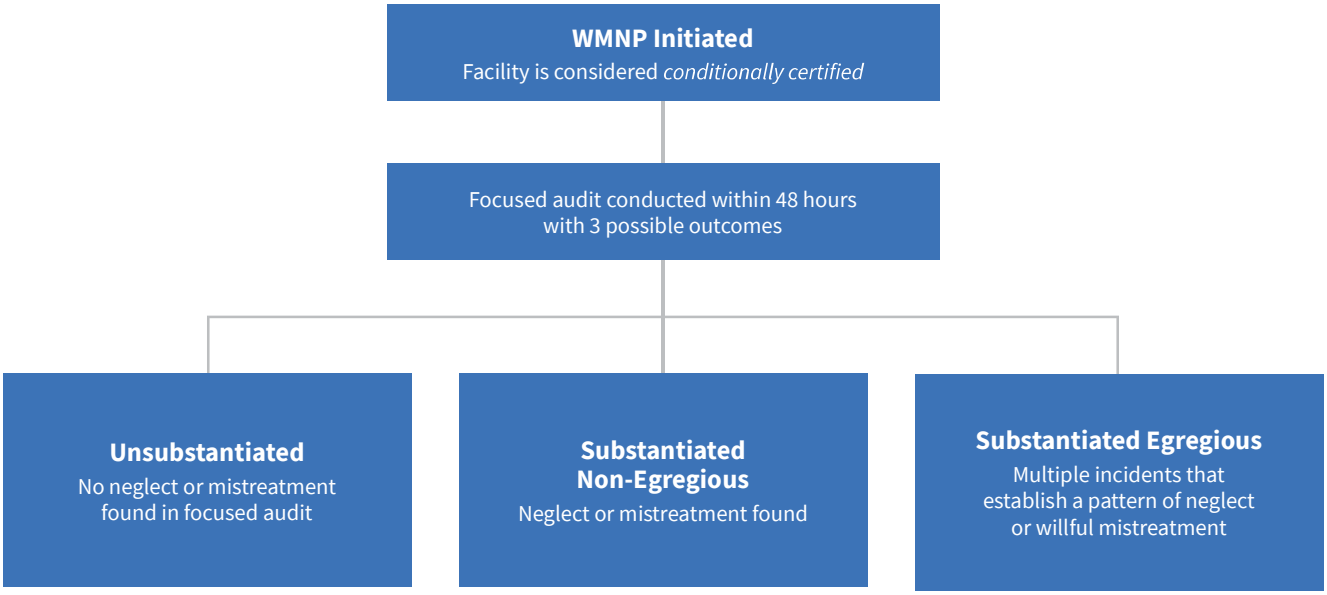
FARM will contact the participant to discuss the credible allegation or evidence presented against their supplying facility.

Protocol process

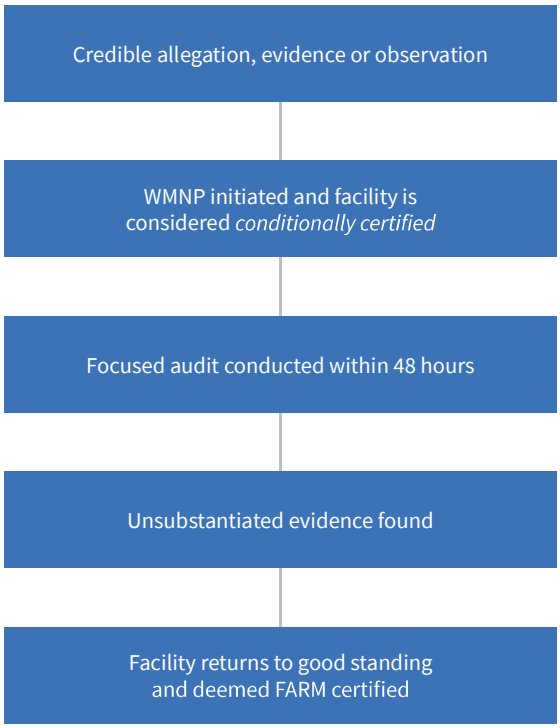
1. The facility will have conditional certification once the protocol is initiated.
2. An audit is required to occur within 48 hours.
3. Based upon the audit, if the allegation or evidence is **found to be unsubstantiated**, the facility will be reinstated to good standing in FARM. The facility returns to the normal evaluation cycle as outlined by FARM's participation agreement.
4. Based upon the audit, if the allegation or evidence is **found to be substantiated but non-egregious**:
   a. Auditor will provide report of findings to FARM, the participant, and the facility; the facility is placed on probation.
   b. The facility and the participant will be provided notification that will detail corrective actions that the facility is required to implement within a defined timeframe as determined by the audit and farm.
   c. During the timeframe while the facility is implementing corrective actions, the facility will remain on probation.
   d. Audit(s) must be conducted to determine that all corrective actions have been satisfactorily addressed within the designated timeframe.
   e. If all corrective actions have been

Appendix 4

After Initiating Willful Mistreatment or Neglect Protocol (WMNP)

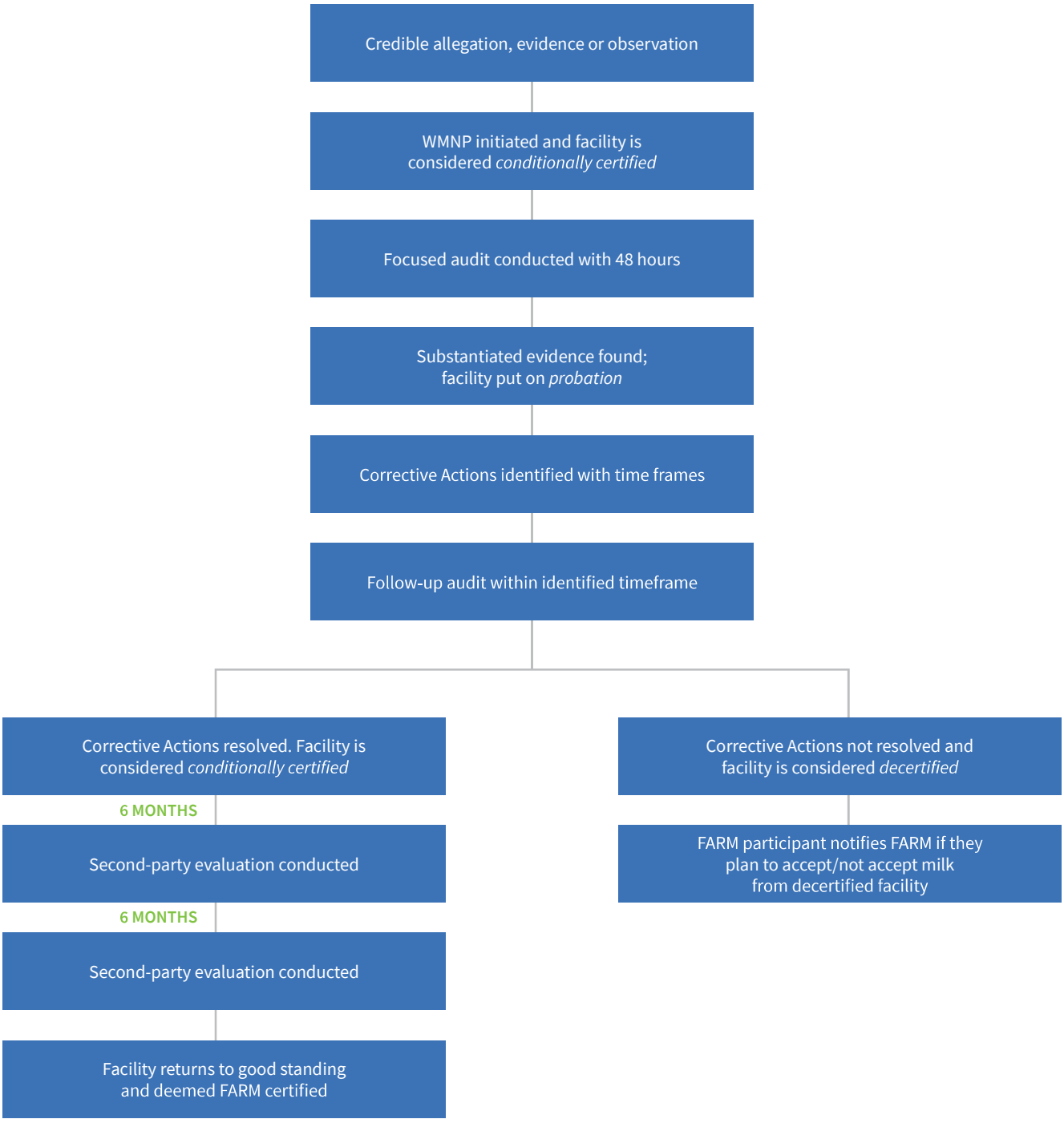


Unsubstantiated Evidence Found



Appendix 4

Substantiated Non-Egregious Evidence Found



addressed satisfactorily according to the follow-up audits(s):

i. The facility will be moved from probation to conditional certification and remain within the protocol.

ii. Follow-up evaluations, preferably conducted unannounced, are required to be conducted 6 months and 12 months after the final audit. Reports from the evaluations are to be provided to FARM, the participant, and the facility.

f. If corrective actions have been satisfactorily addressed based upon the follow-up audit(s) and evaluations

i. The facility will be moved from conditional certification to good standing and the protocol will be satisfactorily completed.

ii. The facility will return to the normal evaluation cycle as outlined by FARM's participation agreement.

g. If corrective actions have not been satisfactorily addressed based upon the follow-up audit(s) and evaluations:

i. Auditor/evaluator will provide report of audit/evaluation findings to FARM, the participant, and the facility.

ii. FARM will notify the participant and the facility that the facility has been decertified.

5. Based upon an audit, if the allegation or evidence is **found to be substantiated and egregious**:

a. Auditor will provide report of findings to FARM, the participant, and the facility.

b. FARM will notify the participant and the facility that the facility has been decertified.

Decertified Facilities

1. Decertified facilities **may not** be accepted into any participant's membership if the participant wishes to remain in good standing with FARM.
2. If a decertified facility is accepted into the membership of a participant, that participant will be immediately delisted as a FARM participant.

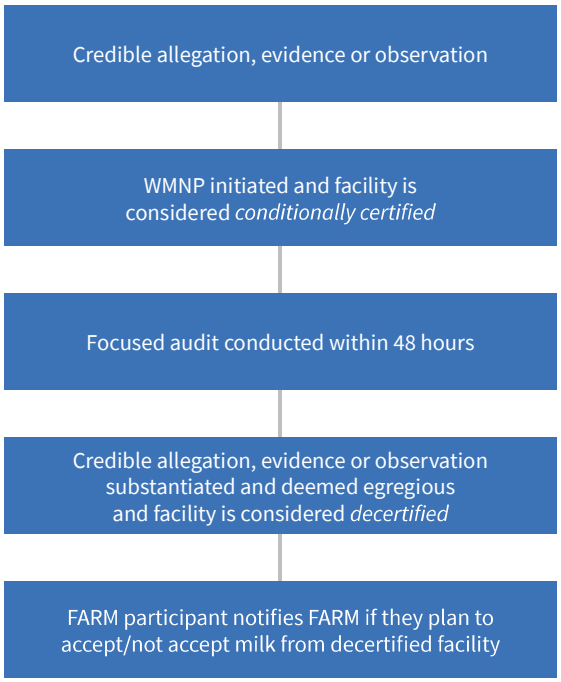
Cooperative/Proprietary Processor Contract Agreement

1. Notwithstanding, FARM recognizes that a participant may immediately terminate a facility's milk supply agreement based upon willful mistreatment or neglect in accordance with their contractual relationship. If the facility's milk supply agreement is terminated for such reason, the facility is no longer in good standing with FARM.
2. If a facility's milk supply agreement has been terminated by a participant based upon willful mistreatment or neglect without previous protocol execution, and then enters into a contract agreement with a different participant, the facility will be considered conditionally certified, and required to undergo the protocol.

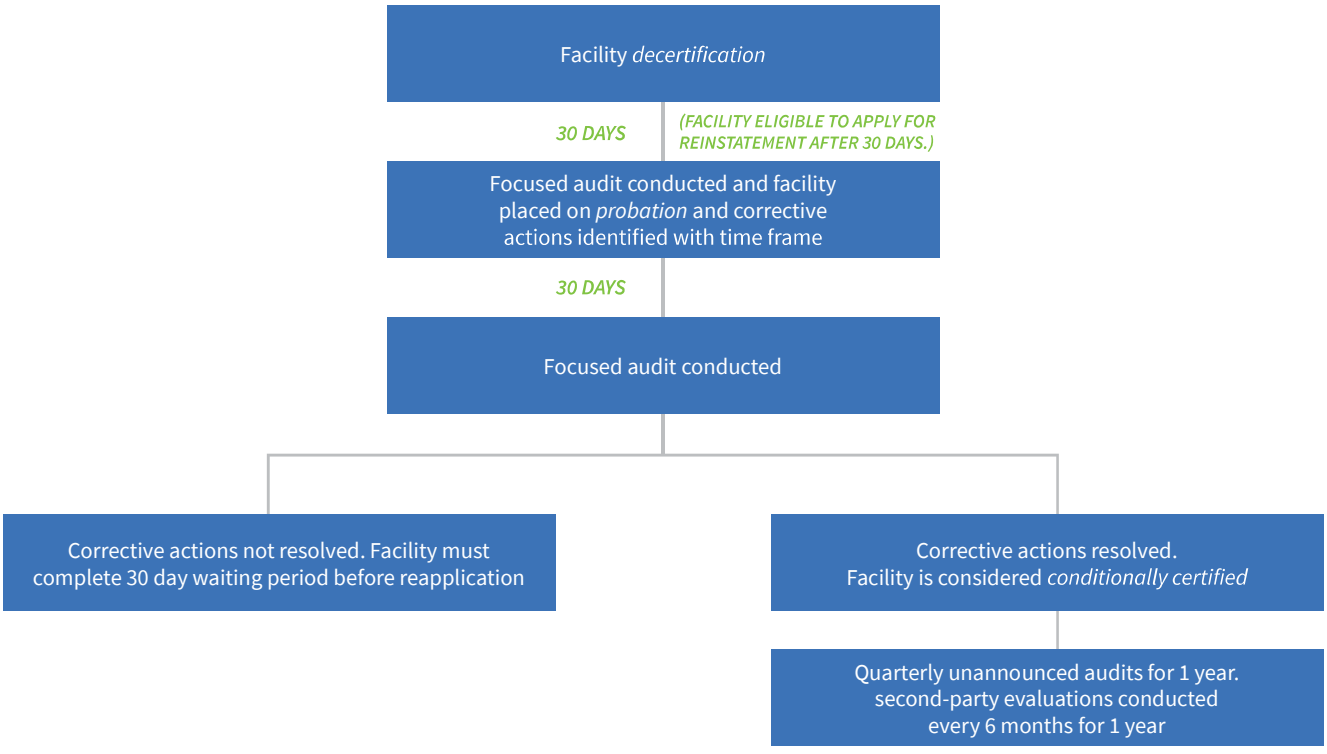
Please see the
National Dairy FARM Program
Animal Care Participant Handbook
for the full Willful Mistreatment
or Neglect Protocol.

Appendix 4

Egregious Evidence Found



Decertified Reinstatement



Appendix D: Training Resource Library & Website

Training Resources & Educational Library

nationaldairyfarm.com/training-resources/

This online resource contains links to external tools for on-farm implementation.

Resource Library

nationaldairyfarm.com/producer-resources/resource-library/

This online library provides comprehensive resources to ensure success in the FARM Program.

Animal Care 4 Evaluation Preparation Guide

This document speaks to the second-party evaluators and third-party verifiers to explain protocols and processes during audits.

Animal Care 4 Participant Handbook

This guide describes the management of the FARM Animal Care Program for participants, the cooperatives or proprietary processors that have signed current participation agreement contract.

For more information, visit the National Dairy FARM Program Website at **nationaldairyfarm.com**.

For questions, contact **dairyfarm@nmpf.org**.

ACRONYMS

AABP	American Association of Bovine
AMDUCA	Animal Medicinal Drug Use Clarification Act
AVC	Academy of Veterinary Consultants
AVMA	American Veterinary Medical Association
BCS	Body Condition Scoring
CIP	Continuous Improvement Plan
DEA	Drug Enforcement Administration
DMI	Dairy Management, Inc.
FARAD	Food Animal Residue Avoidance Databank
FDA	Food and Drug Administration
MCAP	Mandatory Corrective Action Plan
NMPF	National Milk Producers Federation
VCPR	Veterinarian-Client-Patient Relationship
VOR	Veterinarian of Record
WDI	Withdrawal interval

GLOSSARY

For the purposes of the FARM Animal Care reference manual, the following words are defined as follows:

Animal Welfare: How an animal is coping with the conditions it lives in. An animal is in a good state of welfare (as indicated by scientific evidence) if it is healthy, comfortable, well nourished, safe, able to express innate behavior, and it is not suffering from unpleasant states such as pain, fear and distress. Good animal welfare requires disease prevention and veterinary treatment, protection from heat and cold, management and nutrition, humane handling and humane slaughter/euthanasia. Animal welfare refers to the state of the animal; the treatment that an animal receives is covered by other terms such as animal care, animal husbandry and humane treatment.

Banding: The application of an elastic band to cut off blood supply to the scrotum and testicles, which eventually fall from the body.

Best Practice: An animal care guideline, protocol or practice that achieves the desired outcome described by the corresponding management checklist point. More than one best practice may exist for a corresponding outcome. For example, a best practice for an effective record keeping system, which is a FARM Program guideline, may be achieved by keeping written animal health logs or a computer record system like DairyComp 305.

Body Condition Scoring (BCS): A common dairy practice used to determine the nutritional status of an individual heifer or cow, or to evaluate the average condition for a group. Animals are evaluated on a 5-point scale, with 1 being extremely thin and 5 being extremely fat.

Castration: The process of testicle removal or destruction.

Continuous Improvement Plan (CIP): A written plan that identifies animal care improvement area(s). A CIP requires action to be taken to meet the standard within a maximum of three years, but the FARM Animal Care participant/evaluator may set a deadline sooner than three years. Failure to meet the standard within the allotted timeframe will result in the facility being placed on conditional certification, leading to conditional decertification if standards are not met in a 60-day time period. Evaluators and participants can create CIPs for additional standards that have not been designated by FARM.

Cow Care Agreement: An agreement signed by all family and non-family employees with animal care responsibilities indicating that: (1) they have received annual training in animal handling and stockmanship; (2) they agree to care for all animals humanely and with respect and will not participate in animal abuse of any kind, and (3) they will report any abuse to the farm owner or manager should they witness it. This document must be signed annually.

Dehorning: Removal of the horn, per AABP guidelines, after it has attached to the skull (at approximately 8 weeks old).

Disbudding: A procedure, per AABP guidelines, to stop the growth of the horn bud or remove the horn tissue before the horn bud has attached to the calf's skull (less than 8 weeks old).

Distress: Occurs when livestock are injured, sick or in pain.

Dry Cows: Non-lactating pregnant cows from the end of lactation until next parturition. A pregnant cow is generally dry (non-lactating) for a period of 40 to 60 days before the next calving.

Dystocia: A difficult birth typically requiring assistance from the animal caretaker.

Employee with Animal Care Responsibility: A family or non-family employee on the farm responsible for the care of dairy animals.

Failure of Passive Transfer (FPT): The condition when calves do not receive enough colostrum immunity from their dam. In the cattle industry, a common criterion to define FPT is when calves have a serum (or plasma) IgG concentration less than 10 grams per liter at 24 hours of age.

Growing Animals: The period between weaning and first parturition during which an animal grows through puberty and begins to approach maturity, from approximately 6 weeks to 24 months old. See also Bred Heifer, Open Heifer and Springing Heifer.

Herd Health Plan: An animal health management system developed with a veterinarian to prevent, diagnose, control and treat disease or injury of all dairy cattle on a farm.

Hock and Knee Scoring: An assessment for adequacy of bedding and stall comfort for an individual animal or the average condition for a group. Animals are evaluated on a 3-point scale, with 1 being no hair loss or swelling and 3 being severe swelling or lesion.

ISO-Certified Company: A company that has gone through a certification process approved by the International Organization for Standardization (ISO). ISO is a worldwide federation of national standards bodies that creates consistent rules or guidelines of technical specifications.

Lactating Dairy Cow: Any bovine female that has had her first calf.*

Licensed Veterinarian: Licensed by one or more state boards of veterinary medical examiners to practice veterinary medicine within their respective state(s).

Locomotion Scoring: An assessment of lameness for an individual animal or the average condition for a group. Animals are evaluated on a 3-point scale, with 1 being sound and 3 being severely lame.

**This definition is written in such a way that allows FARM Program second-partyevaluators to easily separate different classes of animals for observation and analysis. It is important to note that this definition differs from that of the FDA classification of animals for approved drugs. The FDA classifies such animals as follows: "The term 'non-lactating dairy cattle' includes replacement dairy heifers, replacement dairy bulls, and dairy calves, according to current animal industry standards and a long-standing FDA practice. These classes of dairy cattle have not yet, or would never produce, milk for human consumption. The term non-lactating dairy cattle does not include dry dairy cows. Dry dairy cows have previously produced milk for human consumption and will again in the future after completion of the 'dry period' between lactations."*

Mandatory Corrective Action Plan (MCAP): An MCAP is a written plan that identifies animal care improvement area(s). The timeframe for completion of an MCAP is different than that of a CIP or IAP. MCAPs must be completed within nine months. However, a participant/evaluator may require that a standard be met before the nine-month deadline. Failure to meet these standards within the allotted timeframe will result in the facility being placed on conditional certification, leading to conditional decertification if standards are not met in a 60-day period.

Newborn Calf: A young cow, from birth through colostrum feeding, typically in its first 48 hours of life.

Pain: An unpleasant physical sensation occurring in varying degrees of severity because of injury, disease or from a medical or management procedure.

Patient: An animal that receives medical attention, care or treatment.

Pre-Weaned Calf: A calf fed milk or milk replacer from birth through weaning.

Protocols: Written processes that provide specific instructions to cow-side personnel for performing a single, specific task. As a training tool, written protocols improve communication and work consistency. They may include instructions provided by the VOR for the management of dairy cows in various situations and under various conditions.

Second-Party Evaluation: An external review and assessment of on-farm animal care practices on a participating farm based on the FARM Program guidelines. Participating farms must undergo a second-party evaluation at least once every three years.

Second-Party Evaluator: A trained dairy professional certified by the FARM Program to complete on-farm second-party evaluations. Only qualified individuals who have completed annual FARM certification trainings are qualified to conduct second-party evaluations. Typically, second-party evaluators are co-op/processor staff, veterinarians or independent dairy consultants. Evaluators must have a minimum combination of five years of education — including animal science, dairy science or other relevant curriculum — and/or on-farm dairy experience. Evaluators must apply, complete a phone interview, attend classroom and on-farm training, pass competency exams and recertify annually.

Pre-Fresh Heifers: A heifer that is in the last few weeks of pregnancy.

Stockmanship: The knowledgeable and skillful handling of cattle, based on accepted animal behavior principles, in a safe, efficient, effective and low-stress manner.

Third-Party Verification: A process by which third-party verifiers inspect a representative percentage of participating farms each year to provide statistically verified data regarding adherence to FARM Program guidelines. Once a second-party evaluation is complete, a dairy facility is eligible to be randomly selected, through statistical sampling, to undergo third-party verification. Statistical sampling includes selection criteria like FARM participant geographic location, size and operation type to ensure that the number of randomly selected dairy farms mirrors participants in the entire program. Verification helps ensure the program accomplishes its goals and objectives by confirming the second-party evaluators are upholding the integrity of program implementation.

Third-Party Verifier: A trained and qualified person who does not have a conflict of interest in the operation or the outcome of the verification process. Third-party verifiers must meet the same qualifications as second-party evaluators.

Veterinarian-Client-Patient Relationship (VCPR): The FARM Program uses the AABP definition of VCPR. See Chapter 2: Veterinarian Review for the full definition.

Veterinarian of Record (VOR): The VOR is the party responsible for providing appropriate oversight of drug use on the farm. Oversight is a critical component of establishing, maintaining and validating a VCPR. Oversight should include, but may not be limited to: establishing treatment protocols, personnel training, treatment records review, drug inventory monitoring and assuring appropriate labeling of drugs.

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UNITED STATES
National Residue Program for Meat, Poultry, and Egg Products

FY 2016 RESIDUE SAMPLE RESULTS[1]

United States Department of Agriculture
Food Safety and Inspection Service
Office of Public Health Science

May 2017

[1] Cover October 2015 through September 2016

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Preface

The “2016 Food Safety and Inspection Service (FSIS) National Residue Program Data” publication (the ‘Red Book’) explains FSIS’ chemical residue sampling plans and presents National Residue Program (NRP) testing results by fiscal year. [For those reading this electronically, this document has been commonly known as the “Red Book” because the covers of the printed versions are red.] In addition, the following appendices are included for the convenience of the reader: Appendix I, NRP Positive Non-Violative and Positive Violative Residue Samples Results; Appendix II, Statistical Table; Appendix III, FY2016 List of Chemical Residues by Class/Method ;Appendix IV, Summary of Scheduled Sampling Data from 2013 to 2016, Appendix V, Summary of Import Re-inspection Sampling Data from 2013 to 2016 and Appendix VI, Inspector Generated Sampling Data from 2013 to 2016 (includes KIS™ test)

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Contacts and Comments

Personnel from the Science Staff (SciS), within the Office of Public Health Science (OPHS) at the United States Department of Agriculture’s (USDA) Food Safety and Inspection Service (FSIS) coordinated this effort and are responsible for the publication of this material. Questions about the U.S. NRP should be directed to:

USDA/FSIS/OPHS
1400 Independence Avenue, SW
355 E Street - Patriot Plaza III
Washington, D.C. 20250-3700
Questions can be sent to askFSIS:
http://askfsis.custhelp.com/app/utils/login_form/redirect/ask

Principal Authors (USDA/FSIS/OPHS/Science Staff)

Naser Abdelmajid
Randolph Duverna

Executive Summary

The United States National Residue Program (NRP) is comprised of the following programs:

- Domestic Sampling Plan
  - Scheduled
  - Inspector-Generated
- Import Reinspection Sampling Plan

During FY 2016, (October 2015 to September 2016), FSIS reported **922** residue violations **29** stemmed from the Domestic Scheduled Sampling Program and **893** from the Inspector-generated Sampling Program) in **758** samples (**26** under the Domestic Scheduled Sampling Program and **732** under the Inspector-generated Sampling Program). Additionally, FSIS reported **22** residue violations in **2,676** samples under the Import Reinspection Sampling.

By comparison, in FY2015, there were **1,041** residue violations (**17** from the domestic scheduled sampling program and **1,024** from the Inspector-generated sampling program) in **808** samples. Note: Multiple violative (exceeding an acceptable or tolerable level set by FDA and/or EPA) residue may be detected in a single sample.

Domestic Scheduled Sampling

In FY 2016, under the Domestic Scheduled Sampling program, FSIS Inspection Program Personnel (IPP) collected **7,067** residue samples (This includes **6,535** samples from U.S. Federal establishments and **532** from U.S. State plants), from which **29** violative residues were reported from **26** samples, which is less than 1 % of the 6,445 samples collected under the Domestic Scheduled Sampling program. In FY 2015, FSIS IPP collected **6,445** residue samples, from which **17** violative residues were reported from **12** samples (less than 1%).

During FY 2016, four carbadox, two DDT/metabolites , one doramectin, , one ivermectin, two melengestrol acetate, seven moxidectin, one pentachlorobenzene, one permethrin, one piperonyl butoxide, two sulfadimethoxine and seven sulfamethazine violations were reported in the Domestic Scheduled Sampling Program.

In some cases, chemical residues were detected in samples at levels below the set tolerance levels non-violative levels). In FY 2016, **24** samples (less than 1% of **7,067** samples collected) were considered non-violative. By comparison, in FY 2015 the number of non-violative samples was similar, at **23** non-violative positives (less than 1%).

Inspector-generated Sampling

In FY 2016, under the Inspector-generated sampling program, FSIS IPP screened **182,184** samples using the Kidney Inhibition Swab (KIS™) test. Subsequently, **3,649** KIS™ test screened positive samples were submitted to FSIS field laboratories for further analysis. For FY 2016, **883** KIS™ test residue violations analytes were confirmed in **724** KIS™ test samples (Note: multiple residue violations may be found in same samples.

For comparison, in FY2015, FSIS IPP submitted **4,022** (from **184,010** KIS™ test) samples for laboratory confirmation. Of the **4,022** KIS™ submitted **1,017** KIS™ residure violatons were confirmed in **792** samples.

Under the Inspector-generated Sampling Program, samples from show animals, state testing program and collected-generated were sent directly to FSIS labs, for residue Analysis. For FY 2016, under these sampling programs **Ten** additional reside violative analystes were identified in **eight** samples submitted under this unique sampling.

Examination of the FY 2016 Inspector-generated Sampling Program showed that the predominant violative residues were Ceftiofur (**223**), Penicillin (**216**) and Sulfadimethoxine (**76**), which accounts for 25, 24 and 9% of total violative residues, respectively. In FY 2015, the top violative residues were Ceftiofur, Penicillin, and Sulfamethazine.

In FY 2016, **728** samples with non-violative positives were observed in the Inspector-generated Sampling Program, which was down, when compared to the **873** reported in FY 2015.

Import Reinspection Sampling

Of the **2,676** import samples analyzed, under the FY 2016 Import Reinspection Sampling Program, **22** samples had residues exceeding an acceptable or tolerable level set by FDA and/or EPA. These were from samples originating from Nicaragua (**2**) and Uruguay (**20**). In comparison to FY2015, where **seven** samples with violative residues were detected (**2,922** import samples) originating from Brazil (**1**), Canada (**1**), and Nicaragua (**5**).

FSIS continually strives to improve its methods for reporting of NRP data. These reports and previous years' residue sample results are publicly available on the FSIS website at:

http://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-and-reports/chemistry/residue-chemistry

Acronyms

CSI- Consumer Safety Inspector

COLLGEN – Collector-Generated Samples sent directly to the laboratory

DW – FSIS Data Warehouse

EPA- Environmental Protection Agency

FDA- Food and Drug Administration

FSIS – Food Safety and Inspection Service

HACCP – Hazard Critical Control Point

IPP – Inspection Program Personnel

KIS™ Test – Kidney Inhibition Swab Test

MRM – Multi Residue methods

ND – Non-detect

NRP- National Residue Program

OPHS – Office of Public Health Science

PHIS – Public Health Information System

PHV – Public Health Veterinarian

PPB – parts per billion

PPM – parts per million

SAT – Surveillance Advisory Team

STATE – State or Government Agency Testing

SHOW – Show Animals

U.S NRP – U.S**.** National Residue Program

"8888": A numerical entry that indicate instances when chemical residues results were detected, but were not quantitated.

Introduction

The U.S. National Residue Program (NRP) for Meat, Poultry, and Egg Products, administered by the U.S. Department of Agriculture's (USDA), Food Safety and Inspection Service (FSIS), is an interagency program designed to identify, rank, and analyze for chemical contaminants in meat, poultry, and egg products. FSIS publishes the NRP Residue Sampling Plans (traditionally known as the Blue Book) each year to provide information on the process of sampling meat, poultry, and egg products for chemical contaminants of public health concern.

Background

FSIS administers this regulatory program under the Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 et seq.), the Poultry Products Inspection Act (PPIA) (21 U.S.C. 453 et seq.), and the Egg Products Inspection Act (EPIA) (21 U.S.C. 1031 et seq.). The NRP is an important component of FSIS mission to protect the health and welfare of the consumers by regulating the meat, poultry, and egg products produced in federally inspected establishments and to prevent the distribution in commerce of any such products that are adulterated or misbranded.

The NRP requires the cooperation and collaboration of several agencies for its successful design and implementation. FSIS, along with the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) are the primary Federal agencies managing this program. The FDA, under the Federal Food, Drug, and Cosmetic Act (FFDCA), establishes tolerances for veterinary drugs and action levels for food additives and environmental contaminants. The EPA, under the FFDCA, the Federal insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) establishes tolerances for registered pesticides. Title 21 Code of Federal Regulations (CFR) includes tolerance levels established by FDA; and Title 40 CFR includes tolerance levels established by EPA.

The Surveillance Advisory Team (SAT) meets annually to evaluate chemical compounds for inclusion in the NRP scheduled sampling plans. The SAT includes representatives from FSIS, FDA, EPA, USDA's Agricultural Research Service (ARS), and the USDA's Agricultural Marketing Service (AMS), as well as HHS' Centers for Disease Control and Prevention (CDC). The SAT consists of experts in veterinary medicine, toxicology, chemistry, and public health who provide professional advice, as well as information on veterinary drug and pesticide use in animal husbandry. SAT discussions are used to decide which compounds represent a public health concern and warrant inclusion in the NRP scheduled sampling plans. In addition, the SAT may propose, based on professional judgment and reliable field information, the initiation of exploratory assessments for directed sampling on a production class or region of the country. These agencies work together to create the annual sampling plan, based on the following: prior NRP findings of chemical residues in meat, poultry, and egg products; FDA veterinary drug inventories completed during on-farm visits and investigation information; and pesticides and environmental contaminants of current importance to EPA.

Chemical compounds analyzed in the program include approved and unapproved veterinary drugs, pesticides, and environmental compounds. The NRP is designed to: (1) provide a structured process for identifying and evaluating chemical compounds used in food animals; (2) analyze chemical compounds of concern; (3) collect, analyze, and report results; and (4) identify the need for regulatory follow-up subsequent to the identification of violative levels of chemical residues.

Actions taken on violations

FSIS has administered the NRP by collecting and analyzing meat, poultry, and egg product samples for specific chemical compounds at FSIS laboratories since 1967 for meat and poultry, and beginning in 1995 for egg products. A violation occurs when an FSIS laboratory detects a chemical compound level in excess of an established tolerance or action level as well as if the residue detected has no approved tolerance. Once the laboratory analysis is complete, FSIS enters the detailed residue violation information into the Residue Violation Information System (RVIS), an FSIS/FDA interagency database. FSIS provides establishment and the designated FSIS Inspection Program Personnel (IPP) with the analysis results and also notifies the producer via certified letter. Under best practices, the establishment also should notify the producer that an animal from that business has been identified as having a residue violation. In addition, FSIS shares the violation data with EPA and FDA, where the latter Agency has on-farm jurisdiction. FDA and cooperating State agencies investigate producers linked to residue violations and, if conditions leading to residue violations are not corrected, can enforce legal action.

To notify the public and the industry of repeated residue violations by the same producer, FSIS posts a weekly Residue Repeat Violators List on its Web site that identifies producers with more than one violation on a rolling 12-month period. In addition, the list provides helpful information to the AMS-School Lunch Program purchase clearance processors and producers who are working to avoid illegal levels of residues, serves as a deterrent for violators, and enables FSIS and FDA to make better use of resources (list for processors and producers). Because FSIS updates are posted weekly, FDA may not have investigated each violation at the time of publication.

FSIS Laboratory Analytical Methods

In January 1997, FSIS implemented the Hazard Analysis and Critical Control Point (HACCP) inspection system in all federally inspected establishments. The HACCP regulation (HACCP GPO CFR) requires FSIS-inspected slaughter and processing establishments to identify all food safety hazards (including drug residues, chemical contaminants, and pesticides) that are reasonably likely to occur before, during, and after the food animal or product enters the slaughter establishment. The regulation also requires establishments to identify preventive measures to control these hazards. FSIS takes regulatory action against establishments that do not have an effective chemical residue control program in place. Minimizing food safety hazards from farm-to-fork protects consumers from the public health risks associated with chemical contaminants in food.

With greater public concern about the risks of chemical contaminants, focus has increased on strengthening the identification, prioritization, and testing for chemical hazards in meat, poultry, and egg products in the United States. The sampling plan for residues in FSIS-regulated products includes strengthening the focus of public health-based sampling. This approach includes broader screens for veterinary drugs, pesticides, and heavy metals, as well as conducting more analyses per sample.

FSIS uses analytical methods to detect, identify, and quantify residues that may be present in meat, poultry, and processed egg products. The Agency utilizes these methods for monitoring and for surveillance activities to determine product adulteration and for evaluations of human health risk. The Agency uses available methodologies to take appropriate regulatory action against adulterated products in a manner consistent with the reliability of the analytical data. The FSIS Analytical Chemistry Laboratory Guidebook lists the analytical methods used by the agency.

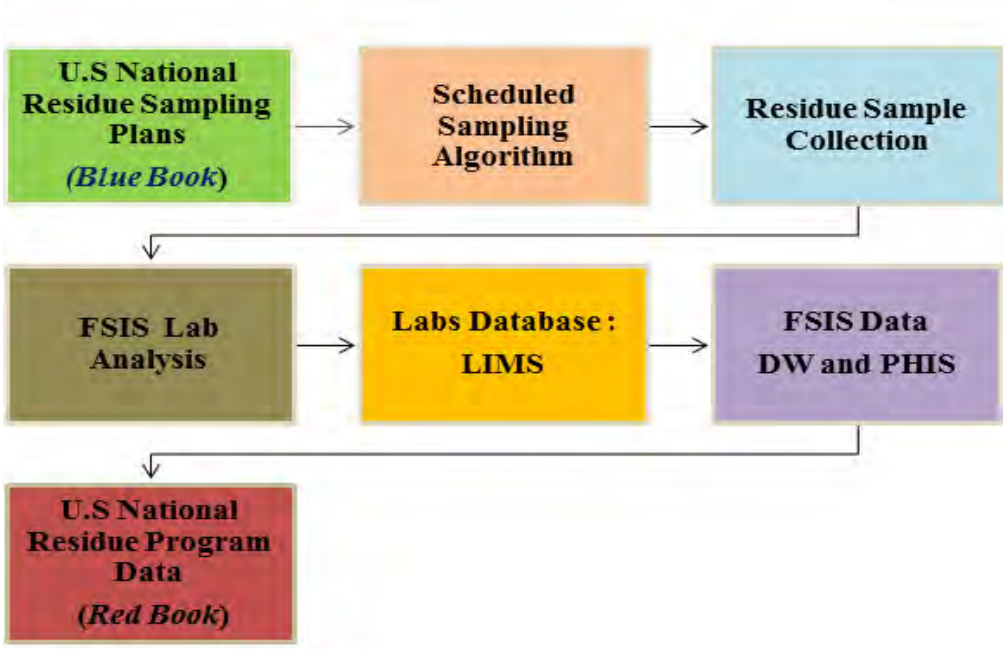

Figure 1. National Residue Program: The figure illustrates the intricate steps of the NRP. The NRP begins with interagency planning (Blue Book) of sampling program, which is followed by collection and analysis of samples reported (Red Book).

Overview of the Sampling Plans

The United States Government Fiscal Year (FY) runs from October 1 through September 30. To match this, since 2012, FSIS switched from implementing the NRP on a Calendar Year (CY) to a FY basis. This change allows the program to run concurrently with the Federal budget cycle.

The NRP consists of three separate, but interrelated, chemical residue testing programs: scheduled sampling (Tier 1), targeted sampling at the production or compound class level (Tier 2), and targeted sampling at the herd/flock or compound class level (Tier 3). This basic structure has been in existence since 1967. These testing programs provide data for FSIS to detect chemical residues of public health concern and have been modified annually in response to emerging chemical residue concerns and improved testing methodologies.

The 2016 NRP Residue Sampling Plan focuses on chemical residues in domestic meat, poultry, and egg products and the import reinspection of meat, poultry, and egg products. The domestic sampling plan includes scheduled sampling and inspector-generated sampling. The import reinspection sampling plan encompasses normal sampling, increased sampling, and intensified sampling. Directive 10,800.1, Rev 1 provides further detail on those sampling procedures.

Domestic Sampling Plan

1. Tier 1

The Tier 1 sampling plan is the scheduled sampling of specified slaughter subclasses at the time of slaughter, after they have passed antemortem inspection. Carcasses are randomly selected for sampling. The number of samples scheduled each year is based on the probability of detecting at least one violation (Appendix II). Data collected from Tier 1 sampling serves as a baseline level for chemical residue exposure. Sampling tasks are assigned each month through the Public Health Information System (PHIS). The sampling task provides information to the Inspection Program Personnel (IPP) on when to collect the sample (collection window) and which production class to sample. The establishment holds or controls livestock carcasses selected for testing pending the results of analysis. For directed testing of poultry, the IPP recommends to the establishment that the establishment holds the specific poultry carcasses selected for residue testing pending the analysis results.

Tier 1 sampling results also can be used to identify producers or other entities marketing animals with violative levels of residues. Thus, the Tier 1 sampling plan not only gathers information, but also assists in deterring practices that lead to violative residues.

In 2016, the Tier 1 sampling plan consisted of random samples collected from each of the following production classes: beef cows, bob veal, dairy cows, steers/ heifers, market hogs, sows, young chickens, and young turkeys. These production classes represent 95 percent of domestic meat and poultry consumption.

2. Tier 2

a. Inspector-Generated Sampling

FSIS inspection program personnel (IPP) conduct inspector-generated sampling when they suspect that animals may have violative levels of chemical residues. Currently, inspector-generated sampling targets individual suspect animals, suspect populations of animals, and animals condemned for specific pathologies listed in FSIS Directive 10,800.1, Rev 1. When Public Health Veterinarians (PHVs) detect evidence of a disease that may have been treated or suspect the administration of a drug, they retain the carcass and analyze samples from those carcasses using an in-plant method to screen for the presence of chemical residues. If the in-plant test is negative for antimicrobial residues included in the screen, the carcass is released to the establishment. If there are screen positive results, the carcass is held pending the results of laboratory testing. The PHV condemns carcasses of animals found to contain violative levels of residues in the muscle or if an unapproved drug is detected in any tissue.

In 2016, IPP completed in-plant residue screens using the Kidney Inhibition Swab test (KIS™ test). The screen positive samples are submitted to the FSIS Midwestern Laboratory and analyzed by the laboratory to identify, quantify and confirm the contaminants.

i. Sampling of Individual Suspect Animals

Under the direction of the PHV, IPP are to conduct a KIS™ test on any carcass that based on herd history or ante-mortem or post-mortem findings inspection findings may contain a violative drug residue. IPP are to follow the instructions provided in Directive 10,800.1, Rev 1, chapter three for circumstances warranting a KIS ™ test and Chapter Four for performing KIS™ tests and documenting the task in PHIS. The PHV selects a carcass for sampling based on the criteria outlined in FSIS Directive 10,800.1, Rev 1 (i.e., animal with disease signs and symptoms, producer history, or as a follow-up to results from random scheduled sampling). Usually, the sample is screened in the plant by the IPP and the screen-result verified when necessary by a PHV. Other samples are sent directly to the laboratory for analysis. For example, if the IPP suspects the misuse of a veterinary drug in an animal, she/he can perform the relevant in-plant screening analysis. If the result of a screening analysis is positive, the carcass is held (if it is not already condemned for other pathology or conditions that would make it unfit for human consumption), and the liver, kidney, and muscle samples from the carcass are then sent to an FSIS laboratory for analysis and confirmation.

ii. Sampling of Suspect Animal Populations

Sampling for suspect animal populations is directed by an FSIS regulation (9 CFR 310.21) and Directive 10,800.1, Rev 1. This is outlined for healthy appearing bob veal calves and show animals.

b. Targeted Sampling

FSIS implements targeted sampling plans (exploratory assessments) in response to information (obtained by FDA and EPA and provided to FSIS) about misuse of animal drugs and/or exposure to environmental chemicals, as well as in response to Tier 1 analytical results. The duration of these sampling plans vary based on the situation. FSIS may conduct studies to develop information on the frequency and concentration at which some residues like trace metals and industrial components may be inadvertently present in animals. These sampling plans could be designed to distinguish components of meat, poultry and egg products in which residue problems exist, to measure the extent of problems, and to evaluate the impact of actions taken to reduce the occurrence of residues in the food animal population.

Sampling tasks are assigned through PHIS. The sampling task provides instructions to the IPP on when to collect the sample (collection window) and which slaughter production class to collect from. The establishment holds or controls livestock carcasses selected for testing pending the test results. For

directed residue testing of poultry, the IPP recommends to the establishment that the establishments hold the specific poultry carcasses selected for residue testing pending the test results.

In 2016, targeted sampling included old breeder turkeys, and sheep, goats.

3. Tier 3

The Tier 3 sampling plan is similar in structure to the targeted sampling (exploratory assessment) program in Tier 2, with the exception that Tier 3 will encompass targeted testing at a herd or flock level. A targeted testing program designed for livestock or flocks originating from the same farm or geographic region may be necessary on occasion to determine the level of exposure to a chemical or chemicals. For instance, producers may administer some veterinary drugs to a herd or a flock (for example, growth promotants or antibiotics given in the feed) in a way that involves misuse. In addition, livestock and birds may be exposed unintentionally to an environmental contaminant. Therefore, a targeted testing program designed for livestock or flocks originating from the same farm or region may be necessary on occasion to determine the level of a chemical or chemicals to which the livestock or the birds in the flock have been exposed. Tier 3 will provide a vehicle for developing information that will support future policy development within the NRP.

In FY 2016, no Tier 3 sampling was performed.

Import Reinspection Sampling Plan

Imported meat, poultry, and egg products are sampled through the port-of-entry Import Reinspection Sampling Plan, a chemical residue monitoring program conducted to verify the equivalence of inspection systems in exporting countries to the United States standards. All imported products are subject to reinspection, and one or more types of inspection (TOI) are conducted on every lot[2] of product before it enters the U. S. Chemical residue sampling is included in the reinspection of imported products. The following three levels of chemical residue reinspection include:

- normal sampling: random sampling from a lot;
- increased sampling: above-normal sampling resulting from an Agency management decision; and
- intensified sampling: additional samples taken when a previous sample for a TOI that failed to meet U. S. requirements.

The data obtained from laboratory analyses are entered into PHIS, an FSIS database designed to generate reinspection assignments, receive and store results, and compile histories for the performance of foreign establishments certified by the inspection system in the exporting country.

The import reinspection sampling program is structured using the Tier 1 and Tier 2 criteria used to develop the domestic plan. In FY2016, FSIS collected approximately 2676 import samples.

[2] An import lot is a group of products defined statistically and/or scientifically by production segments and certified from one country, one establishment. A lot consists entirely of the same species, process category, and product standard of identity (sub-category). A single lot can contain shipping cartons with varying sizes of immediate containers.

Policy and procedures for holding or controlling product under NRP

As of February 2013, the Agency requires official establishments and importers of record to hold or maintain control of lots of product tested for adulterants until acceptable results become available. FSIS stated that the policy would apply to livestock carcasses subject to FSIS testing for residue on domestic products. FSIS explained that it will not hold poultry carcasses pending test results for residues due to historically low residue problems and large lot size. This was outlined in a published Federal Register Notice 76 FRN 19955.

The Hold and Test policy also applies to normal and increased import reinspection sampling. Additionally, for intensified import sampling, the lot must be retained pending laboratory results.

Domestic Scheduled Sampling Program

This section reports the summary results from the FSIS Domestic Scheduled Sampling Plan. The summary results are associated with specific Animal Class. All data reported in the following tables were collected from the FSIS Data Warehouse and PHIS databases.

Table 1 identifies the animal classes and methods/chemical classes which are in the 2016 NRP

Table 2 summarizes the number of Domestic Scheduled samples and Inspector-generated samples tested by animal class.

Table 3 summarizes the number of residue Domestic Scheduled samples analyzed by animal class, including summary results.

Table 4 summarizes the number of residue Domestic Scheduled samples tested per chemical method by animal class.

Table 5 summarizes Domestic Scheduled Sampling -number of chemical analyses tested per chemical method by animal class.

Table 6 summarizes domestic scheduled sampling violation results by animal class.

Note: Residue detected results with "**8888**" indicate instances when residues were detected, but were not quantitated.

Summary of Domestic Residue Sampling Program

Table 1. FY 2016 Tier I and II List of Animal Class by Method/Chemical Class (Analyses Performed)

Animal Category	Animal Class	Chemical Class Oct 2015- Sep 2016									
		Aminoglycosides	Arsenic	Avermectins	βeta-Agonists	Carbadox	Hormones	Metals	MRM	Nitrofurans	Pesticides
Bovine	Beef Cows	√	√	√	√	--	√	√	√	--	√
	Bob Veal	√	√	√	√	--	√	√	√	--	√
	Dairy Cows	√	√	√	√	--	√	√	√	--	√
	Heifers	√	√	√	√	--	√	√	√	--	√
	Steers	√	√	√	√	--	√	√	√	--	√
Porcine	Market Swine	√	√	√	√	--	--	√	√	--	--
	Roaster Swine	√	√	√	-	√	--	√	√	--	√
	Sows	√	√	√	√	--	--	√	√	--	√
Poultry	Mature Turkeys	√	√	--	--	--	--	√	-	√	--
	Young Chickens	√	√	--	--	--	--	√	√	√	√
	Young Turkeys	√	√	--	--	--	--	√	√	√	√
Minor Species	Goats	√	√	√	--	--	--	--	√	--	--
	Sheep	√	√	√	--	--	--	--	√	--	--

Table 2. FY 2016 Number of Scheduled Residue Samples Tested, by Animal Class

Animal Category	Animal Class	Domestic Scheduled Sampling		Inspector-generated Sampling Tier-2 Suspect Animals	
		Tier-1 & Tier- 2* U.S. Federal Plants	Tier-1 U.S. State Plants	KIS™ Test	COLLEGEN/ SHOW/STATE *
Bovine	Beef Cows	670	60	15,936	12
	Bob Veal	574	--	23,333	4
	Bulls	--	--	1,618	2
	Dairy Cows	720	19	99,660	23
	Formula-Fed Veal	--	--	640	--
	Heavy Calves	--	--	426	--
	Heifers	397	129	2,537	6
	Non-Formula-Fed Veal	--	--	161	--
	Steers	366	145	8,705	16
Porcine	Boars/Stags	--	--	99	--
	Market Swine	684	116	18,754	46
	Roaster Swine	281	--	1,527	--
	Sows	733	36	6,461	3
Poultry	Mature Turkeys**	93	--	--	--
	Young Chickens	742	18	--	--
	Young Turkeys	648	9	--	--
	Goats**	337	--	618	7
Minor Species	Lambs**	--	--	1,224	10
	Sheep**	290	--	485	--
	Total	**6,535**	**532**	**182,184***	**129**

* An additional **129** inspector-generated samples were collected and sent to FSIS labs for analysis. These samples are associated with project codes: **75** COLLGEN, **42** SHOW, and **12** STATE, samples.

** Animal Classes associated with NRP Tier 2 domestic sampling

Table 3. FY 2016 NRP Domestic Scheduled Samples Analyzed by Animal Class – and Summary Results

Animal Category	Animal Class	Number of Non-Detect Samples	Number of Non-Violative Positives Samples	Number of Violative Samples	Total Samples
Bovine	Beef Cows	727	2	**1**	730
	Bob Veal	568	3	**3**	574
	Dairy Cows	736	--	**3**	739
	Heifers	519	5	**2**	526
	Steers	507	4	--	511
Porcine	Market Swine	798	2	--	800
	Roaster Swine	271	4	**6**	281
	Sows	765	3	**1**	769
Poultry	Mature Turkeys	93	--	--	93
	Young Chickens	759	1	--	760
	Young Turkeys	657	--	--	657
Minor Species	Goats	330	--	**7**	337
	Sheep	287	--	**3**	290
	Total	**7017**	**24**	**26**	**7,067**

Note: The results include Tier 1 and Tier 2 animal classes
Data Source: FSIS Data Warehouse and PHIS databases.

Table 4. FY2016 NRP Residue Scheduled Samples -Number of Residue Samples Tested Per Chemical Method by Animal Class

Animal Class (# Samples Collected)	Number of Samples per Chemical Method									
	Aminoglycosides	Arsenic	Avermectins	βeta-Agonists	Carbadox	Hormones	Metals	MRM	Nitrofurans	Pesticides
Beef Cows (730)	725	397	392	289	--	357	114	730	--	286 **(1)**
Bob Veal (574)	571	326	323 **(1)**	216	--	294	118	574 **(2)**	--	211
Dairy Cows (739)	737	395	392	302	--	348	112	739 **(2)**	--	304 **(1)**
Heifers (526)	524	313	310	180	--	294 **(2)**	114	526	--	177
Steers (511)	510	306	303	175	--	276	107	511	--	175
Market Swine (800)	798	447	442	150	2	--	127	799	--	333
Roaster Swine (281)	280	65	64	--	215 **(4)**	--	17	281 **(2)**	--	--
Sows (769)	764	427	421	135	-	1	111	769	--	290 **(1)**
Mature Turkeys (93)	1	1	--	--	--	--	93	1	--	--
Young Chickens (760)	759	408	--	--	--	--	155	760	340	316
Young Turkeys (657)	656	371	1	--	--	--	154	657	275	141
Goats (337)	260	195	198 **(7)**	1	--	--	--	337	--	141
Mature Sheep (290)	200	155	153 **(1)**	1	--	--	--	290	--	131 **(2)**
Total (7,067)	**6,785**	**3,806**	**2,999**	**1,449**	**217**	**1,570**	**1,222**	**6,974**	**615**	**2,505**

Note: Number of violative samples **(in parenthesis)**
Data Source: FSIS Data Warehouse and PHIS databases.

Table 5. FY 2016 NRP Residue Scheduled Samples - Number of Chemical Analytes Tested Per Chemical Method by Animal Class

Animal Class (# Samples Collected)	Number of Chemical Analytes per Chemical Method										
	Aminoglycosides	Arsenic	Avermectins	βeta-Agonists	Carbadox	Hormones	Metals	MRM	Nitrofurans	Pesticides	Total
Beef Cows (730)	7,259	397	1,958	1,732	--	1,785	1,198	58,305	--	24,417	97,051
Bob Veal (574)	5,728	326	1,612	1,296	--	1,470	1,361	46,094	--	17,751	75,638
Dairy Cows (739)	7,379	395	1,960	1,808	--	1,740	1,235	59,252	--	25,724	99,493
Heifers (526)	5,249	313	1,550	1,061	--	1,468	1,397	42,138	--	14,832	68,008
Steers (511)	5,109	306	1,513	1,033	--	1,380	1,262	41,071	--	14,647	66,321
Market Swine (800)	7,999	447	2,205	896	2	--	1,480	69,240	--	28,134	110,403
Roaster Swine (281)	2,836	65	320	--	215	--	298	28,137	--	--	31,871
Sows (769)	7,658	427	2,102	805	-	5	1,081	67,045	--	24,516	103,639
Mature Turkeys (93)	10	1	--	--	--	--	1,008	93	--	--	1,112
Young Chickens (760)	7,599	408	--	--	--	--	1,743	64,022	1,700	26,716	102,188
Young Turkeys (657)	6,569	371	5	--	--	--	1,925	54,081	1,374	21,110	85,435
Goats (337)	2,600	195	984	6	--	--	--	28,061	--	11,826	43,672
Mature Sheep (290)	2,000	155	762	2	--	--	--	23,260	--	11,115	37,294
Total (7,067)	**67,995**	**3,806**	**14,971**	**8,639**	**217**	**7,848**	**13,988**	**580,799**	**3,074**	**220,788**	**922,125**

Note: Multiple analytes may be associated with the same sample. Not all samples are tested for all chemical method. Number of samples per chemical method is indicated in Table 4

Data Source: FSIS Data Warehouse and PHIS databases.

Table 6. FY 2016 Domestic Scheduled Sampling Plan Violations

Animal	Tissue	Compound	Concentration	Units	Tolerance Level Value	Authority (CFR Citation)
Beef Cow	Muscle	Piperonyl Butoxide	0.162	ppm	0.1	40 CFR 180.127
Bob Veal	Muscle	Sulfamethazine	22.500	ppm	0.1	21 CFR 556.670
Bob Veal	Muscle	Sulfamethazine	0.190	ppm	0.1	21 CFR 556.670
	Liver	Sulfamethazine	0.304	ppm	0.1	21 CFR 556.670
Bob Veal	Muscle	Moxidectin	16.1	ppb	0	21 CFR 556.426
Dairy Cow	Liver	Sulfadimethoxine	0.114	ppm	0.1	21 CFR 556.640
Dairy Cow	Liver	Sulfadimethoxine	1.064	ppm	0.1	21 CFR 556.640
Dairy Cow	Muscle	Permethrin (Cis and Trans)	0.213	ppm	0.1	40 CFR 180.378
Heifer	Muscle	Melengestrol Acetate	2.2	ppb	None	21 CFR 556.380
Heifer	Muscle	Melengestrol Acetate	1.3	ppb	None	21 CFR 556.380
Roaster Swine	Liver	Sulfamethazine	0.702	ppm	0.1	21 CFR 556.670
	Muscle	Sulfamethazine	0.237	ppm	0.1	21 CFR 556.670
Roaster Swine	Liver	Carbadox	78.035	ppb	30	21 CFR 556.100
Roaster Swine	Liver	Carbadox	131.001	ppb	30	21 CFR 556.100
Roaster Swine	Liver	Carbadox	31.406	ppb	30	21 CFR 556.100
Roaster Swine	Liver	Carbadox	68.511	ppb	30	21 CFR 556.100
Roaster Swine	Muscle	Sulfamethazine	0.117	ppm	0.1	21 CFR 556.670
	Liver	Sulfamethazine	0.227	ppm	0.1	21 CFR 556.670
Sow	Muscle	DDT and Metabolites	***			
Goat	Muscle	Moxidectin	77.05	ppb	Not Approved	21 CFR 556.426
Goat	Muscle	Moxidectin	29.45	ppb	Not Approved	21 CFR 556.426
Goat	Muscle	Moxidectin	48.4	ppb	Not Approved	21 CFR 556.426
Goat	Muscle	Moxidectin	30.9	ppb	Not Approved	21 CFR 556.426

Table 6. FY 2016 Domestic Scheduled Sampling Plan Violations – Federal Plants

Animal	Tissue	Compound	Concentration	Units	Tolerance Level Value	Authority (CFR Citation)
Goat	Muscle	Moxidectin	56.8	ppb	Not Approved	21 CFR 556.426
Goat	Muscle	Ivermectin	72.45	ppb	Not Approved	21 CFR 556.344
Goat	Liver	Moxidectin	224	ppb	Not Approved	21 CFR 556.426
Sheep	Muscle	DDT and Metabolites	***			
Sheep	Muscle	Pentachlorobenzene	***			
Sheep	Muscle	Doramectin	168.5	ppb	30	21 CFR 556.225

Note:
******:** Violative residue results were residue were detected but not quantified
Not Approved- Residue detected is not approved per species

Data Source: FSIS Data Warehouse and PHIS databases.

Summary of Domestic Inspector -Generated Sampling Program

PHVs, and CSIs under the guidance of a PHV, conduct Inspector-generated residue sampling when an animal is suspected to have undergone drug treatment and may possibly contains violative levels of chemical residues. The PHVs and CSIs also are encouraged to collect samples for residue testing at the FSIS labs when a chemical contamination is suspected. Samples are screened using the KIS™ test. If KIS™ test kits are not available; the PHV submits the sample to the FSIS laboratory for testing.

Table 7 summarizes the total number in-plants screens tests using the KIS™ test, which includes the number of in-plants screens with negative results, number of positive screens sent to FSIS labs for conformation, and the number of carcasses with violations for each animal class.

Table 8 summarizes the total number of samples analyzed and the number of carcasses with violations for each animal class under additional inspector-generated program projects such as COLLGEN, SHOW, and STATE.

Table 9 summarize the results for specific chemical compounds that were detected **(violative**) within inspector-generated sampling project (including the KIS™) across animal class.

Table 10 summarize the results for specific chemical compounds that were detected (**non-violative**) within inspector-generated sampling project (including the KIS™) across animal class.

Note: Data in this document were obtained from the FSIS Data Warehouse and PHIS databases.

Table 7. FY 2016 Tier II Inspector Generated Sampling (KIS ™) Test

Animal Category	Animal Class	KIS ™ Test			
		Total Number of In-plant Samples	Number of In-plant Negative Samples	Number of In-plant Positive Samples	Number of Samples With Confirmed Lab Violations
Bovine	Beef Cows	15,936	15,582	354	**51**
	Bob Veal	23,333	22,961	372	**103**
	Bulls	1,618	1,565	53	**13**
	Dairy Cows	99,660	97,384	2276	**480**
	Formula-Fed Veal	640	627	13	**1**
	Heavy Calves	426	404	22	**9**
	Heifers	2,537	2,486	51	**5**
	Non-Formula-Fed Veal	161	157	4	**0**
	Steers	8,705	8,530	175	**33**
Porcine	Boars/Stags	99	98	1	**0**
	Market Swine	18,754	18,579	175	**4**
	Roaster Swine	1,527	1,507	20	**1**
	Sows	6,461	6,354	107	**21**
Minor Species	Goats	618	614	4	**0**
	Lambs	1,224	1,212	12	**2**
	Sheep	485	475	10	**1**
	Total	**182,184**	**178,535**	**3,649**	**** 724**

**** 883** KIS ™ test violative analytes in **724** lab confirmed KIS ™ test violative samples**.** Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).

Data Source: FSIS Data Warehouse and PHIS databases.

Table 8. FY 2016 Tier II Inspector-Generated Sampling (COLLGEN/ STATE/ SHOW) Projects

Animal Category	Animal Class	COLLGEN		SHOW		STATE	
		Number of Samples	**Number of Samples With Confirmed Lab Violations**	Number of Samples	**Number of Samples With Confirmed Lab Violations**	Number of Samples	**Number of Samples With Confirmed Lab Violations**
Bovine	Beef Cows	7	--	--	--	5	**1**
	Bob Veal	4	**2**	--	--		--
	Bulls	1	--	--	--	1	--
	Dairy Cows	23	**2**	--	--	--	--
	Formula-Fed Veal	--	--	--	--	--	--
	Heavy Calves	--	--	--	--	--	--
	Heifers	5	**1**	--	--	1	--
	Non-Formula-Fed Veal	--	--	--	--	--	--
	Steers	4	--	11	--	1	--
Porcine	Boars/Stags	--	--	--	--	--	--
	Market Swine	22	--	21	**1**	3	--
	Roaster Swine	--	--	--	--	--	--
	Sows	3	--	--	--	--	--
Minor Species	Goats	3	--	4	--	--	--
	Lambs	3	--	6	--	1	**1**
	Sheep	--	--	--	--	--	--
	Total	**75**	**5**	**42**	**1**	**12**	**2**

Note: Results include two violative residues from two dairy cow (penicillin, florfenicol and sulfamethazine), two bob veal (penicillin and sulfamethazine), a beef cow (desfuroylceftiofur) and one heifer (sulfadimethoxine), one market swine (sulfamethazine) and a lamb (penicillin).

Data Source: FSIS Data Warehouse and PHIS databases.

Table 9. FY 2016 Number of Residue Violations results in Inspector Generated Sampling by Chemical Residue and Animal Class (include KIS ™ test, COLLGEN/ STATE/ SHOW project codes)

Chemical Residue	Beef Cows	Bob Veal	Bulls	Dairy Cow	Formula Fed Veal	Heavy Calves	Heifer	Steers	Market Swine	Roaster Swine	Sows	Lamb	Sheep	Total
Amikacin	--	--	--	1	--	--	--	--	--	--	--	--	--	**1**
Ampicillin	--	--	--	28	--	--	--	--	--	--	--	--	--	**28**
Cefazolin	--	--	--	1	--	--	--	--	--	--	--	--	--	**1**
Ciprofloxacin	--	--	1	1	--	1	--	1	--	--	1	--	--	**5**
Desethylene Ciprofloxacin	--	1	--	--	--	--	--	--	--	--	--	--	--	**1**
Desfuroylceftiofur	13	7	3	192	--	--	2	6	--	--	--	--	--	**223**
Dihydrostreptomycin	--	2	--	3	--	--	--	--	--	--	--	--	--	**5**
Enrofloxacin	--	1	--	--	--	--	--	--	--	--	--	--	--	**1**
Florfenicol	15	2	8	11	--	6	--	7	--	--	--	--	--	**49**
Flunixin	6	6	1	49	--	1	2	3	--	--	2	1		**71**
Gentamycin Sulfate	4	--	--	4	--	--	--	3	--	--	--	--	1	**12**
Ketoprofen	--	--	--	2	--	--	--	--	--	--	--	--	--	**2**
Lincomycin	--	--	--	5	--	--	--	--	--	--	--	--	--	**5**
Meloxicam	--	--	1	3	--	--	--	--	--	--	--	--	--	**4**
Moxidectin	1	--	--	--	--	--	--	--	--	--	--	--	--	**1**

Note: Multiple violative analytes in different tissue types may be associated with a single sample (carcass).

Data Source: FSIS Data Warehouse and PHIS databases.

Table 9. FY 2016 Number of Residue Violations results in Inspector Generated Sampling by Chemical Residue and Animal Class (include KIS ™ test, COLLGEN/ STATE/ SHOW project codes) (*cont.*)

Chemical Residue	Beef Cows	Bob Veal	Bulls	Dairy Cow	Formula Fed Veal	Heavy Calves	Heifer	Steers	Market Swine	Roaster Swine	Sows	Lamb	Sheep	Total
Neomycin	--	57	--	2	--	2	--	3	--	--	--	--	--	**64**
Oxyphenylbutazone	--	--	--	--	--	--	--	1	--	--	--	--	--	**1**
Oxytetracycline	2	--	3	8	--	--	--	--	--	--	--	--	--	**13**
Penicillin	18	13	1	153	1	1	--	9	1	1	16	2	--	**216**
Phenylbutazone	1	--	--	--	--	--	--	--	--	--	--	--	--	**1**
Ractopamine	--	--	--	--	--	--	--	1	--	--	--	--	--	**1**
Sulfadiazine	--	2	--	--	--	--	--	--	--	--	--	--	--	**2**
Sulfadimethoxine	3	5	--	67	--	--	1	--	--	--	--	--	--	**76**
Sulfadoxine	--	--	1	4	--	--	--	--	--	--	1	--	--	**6**
Sulfamethazine	5	16	2	27	--	4	--	8	5	--	1	--	--	**68**
Sulfamethoxazole	--	5	--	1	--	--	--	--	--	--	--	--	--	**6**
Sulfamethoxypyridazine	--	--	--	1	--	--	--	--	--	--	--	--	--	**1**
Tetracycline	--	--	--	1	--	--	--	--	--	--	--	--	--	**1**
Tilmicosin	6	3	1	8	--	2	1	3	--	--	--	--	--	**24**
Tylosin	1	--	--	2	--	--	--	1	--	--	--	--	--	**4**
Total	**75**	**120**	**22**	**574**	**1**	**17**	**6**	**46**	**6**	**1**	**21**	**3**	**1**	**893**

Note: Multiple violative analytes in different tissue types may be associated with a single sample (carcass)
Data Source: FSIS Data Warehouse and PHIS databases.

Table 10. FY 2016 Number of Non-Violative results in Inspector Generated Sampling by Chemical Residue and Animal Class (include KIS ™ test, COLLGEN/ STATE/ SHOW project codes)

Chemical Residue	Beef Cows	Bob Veal	Bulls	Dairy Cows	Formula - Fed Veal	Heavy Calves	Heifers	Non Formula - Fed Veal	Steer	Boar/Stag	Market Swine	Roaster Swine	Sows	Lambs	Total
Chlortetracycline	1	--	1	--	--	--	--	1	--	--	2	--	--	--	**5**
Desfuroylceftiofur	--	--	--	18	--	--	--	--	2	--	--	--	--	--	**20**
Dihydro Streptomycin	--	--	--	2	--	--	--	--	--	--	--	--	--	--	**2**
Dihydrostreptomycin	--	--	--	1	--	--	--	--	--	--	--	--	--	--	**1**
Enrofloxacin	1	--	1	1	--	1	--	--	2	--	2	--	2	--	**10**
Eprinomectin	3	--	--	14	--	--	2	--	3	--	--	--	--	--	**22**
Fenbendazole	--	--	--	4	--	--	--	--	--	--	--	--	--	--	**4**
Fenbendazole sulfone	1	--	--	2	--	--	--	--	--	--	--	--	--	--	**3**
Florfenicol	3	--	1	6	--	--	--	--	3	--	--	--	--	--	**13**
Flunixin	3	--	1	40	--	1	1	--	1	--	--	--	3	--	**50**
Gamithromycin	2	--	--	6	--	1	1	--	2	--	--	--	--	--	**12**
Ivermectin	--	--	1	--	--	--	--	--	--	--	--	--	--	--	**1**
Lincomycin	--	--	--	--	--	--	--	--	--	--	15	--	5	--	**20**

Note: Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).

Data Source: FSIS Data Warehouse and PHIS databases.

Table 10. FY 2016 Number of Non-Violative results in Inspector Generated Sampling by Chemical Residue and Animal Class (include KIS ™ test, COLLGEN/ STATE/ SHOW project codes) (*cont.*)

Chemical Residue	Beef Cows	Bob Veal	Bulls	Dairy Cows	Formula - Fed Veal	Heavy Calves	Heifers	Non Formula - Fed Veal	Steer	Boar/Stag	Market Swine	Roaster Swine	Sows	Lambs	Total
Moxidectin	2	--	1	--	--	--	--	--	--	--	--	--	--	--	**3**
Neomycin	3	25	--	8	--	3	--	1	4	--	--	--	--	--	**44**
Oxytetracycline	38	29	9	61	--	4	1	--	7	--	--	--	3	1	**153**
Penicillin	6	2	2	71	1	--	--	--	3	--	--	--	--	--	**85**
Pirlimycin	--	1	--	10	--	--	--	--	--	--	--	--	--	--	**11**
Ractopamine	--	--	--	--	--	--	--	--	1	--	5	--	--	--	**6**
Spectinomycin	4	6	1	19	--	2	1	--	1	--	--	--	--	--	**34**
Sulfadimethoxine	2	--	--	10	--	--	1	--	--	--	--	--	--	--	**13**
Sulfamethazine	--	2	--	3	--	1	--	1	2	--	--	1	--	--	**10**
Tetracycline	3	2	--	30	--	--	--	--	--	--	--	--	--	--	**35**
Tildipirosin	3	--	--	1	--	1	2	--	4	--	--	--	--	--	**11**
Tilmicosin	3	--	1	1	--	--	--	--	--	--	--	1	3	--	**9**
Tulathromycin	29	4	7	36	--	2	16	--	54	1	2	--	--	--	**151**
Total	**107**	**71**	**26**	**344**	**1**	**16**	**25**	**3**	**89**	**1**	**26**	**2**	**16**	**1**	**728**

Note: Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).
Data Source: FSIS Data Warehouse and PHIS databases.

Import Residue Reinspection Sampling Program

In FY2016, FSIS collected 2,676 import samples and analyzed for 169,490 residue analytes from 25 export countries. Twenty Two violations were detected (20 from uruguaw, and two from Nicaragua). For more information, refer to the list of tables below.

Table 11 summarizes the – import number of residue samples tested per chemical method by Production Class and Product Type

Table 12 summarizes the number of import residue samples by inspection level, per exporting country and production type

Table 13 summarizes the number of import residue samples analyzed, by exporting country and Production Type

Table 14 summarizes the number of import residue samples analyzed, number of chemical analyates tested per exporting country and production type

Table 15 summarize number of samples and chemical residues under the import residue sample program, by exporting country

Table 16 summarize import residue sample program (Non-Violative and Violative) results, by exporting country chemical residues and production class

information for countries wanting to import to the United States can be found at:
Importing products to the United States

Information on US products eligible for export can be found at:
Export Library

Table 11. FY 2016 NRP Import Residue Samples - Number of Residue Samples Tested Per Chemical Method by Production Class and Product Type

Methods	Number of Samples Tested										
	Beef		Pork		Veal	Lamb/Mutton	Goat	Chicken		Turkey	
	Fresh	Processed	Fresh	Processed	Fresh	Fresh	Fresh	Fresh	Processed	Fresh	Processed
MRM	252	--	115	--	68	51	22	106	--	60	--
Aminoglycoside	251	--	198	--	68	50	20	107	--	59	--
Pesticides	719	--	128	--	45	50	37	57	--	40	--
Hormones	166	--	--	--	--	--	--	--	--	--	--
βeta-Agonists	110	--	91	--	39	5	1	1	--	--	--
Avermectins	125	117	100	51	25	48	21	--	--	1	--
Arsenic	127	115	100	51	25	48	21	57	31	23	61
Metals	71	18	57	41	24	--	--	41	11	18	24
Sulfonamides	--	32	---	46	1	--	--	1	--	--	24

Data Source: FSIS Data Warehouse and PHIS databases.

Table 12. FY 2016 Number of Import Residue Samples by Inspection Level, per Exporting Country and Production Type

Country	Normal		Increased	Intensified		Total
	Fresh	Processed	Processed	Fresh	Processed	
Australia	160	8	--	--	--	**168**
Brazil	64	63	--	--	--	**127**
Canada	517	141	--	--	6	**664**
Chile	142	10	--	--	--	**152**
Costa Rica	12	--	--	--	--	**12**
Denmark	24	9	--	--	--	**33**
Finland	3	--	--	--	--	**3**
France	--	2	--	--	--	**2**
Germany	--	12	--	--	--	**12**
Iceland	48	--	--	--	--	**48**
Ireland	103	--	--	--	--	**103**
Israel	--	85	--	--	--	**85**
Italy	--	11	--	--	--	**11**
Japan	37	--	--	--	--	**37**
Korea, Republic Of	--	1	--	--	--	**1**
Lithuania	5	30	--	--	--	**35**
Mexico	173	20	--	--	2	**195**
Netherlands	16	--	--	--	--	**16**
New Zealand	99	12	--	--	--	**111**
Nicaragua	85	--	4	45	--	**134**
Northern Ireland	15	--	--	--	--	**15**
Poland	16	11	--	--	--	**27**
Spain	47	2	--	--	--	**49**
United Kingdom	58	--	--	--	--	**58**
Uruguay	156	35	179	208	--	**578**
Total	**1,780**	**452**	**183**	**253**	**8**	**2,676**

Data Source: FSIS Data Warehouse and PHIS databases.

Table 13. FY 2016 Number of Import Residue Samples Analyzed, by Exporting Country and Production Type

Country	Production Type											
	Beef		Pork		Veal	Lamb Mutton	Goat	Chicken		Turkey		Total
	Fresh	Processed	Fresh	Processed	Fresh	Fresh	Fresh	Fresh	Processed	Fresh	Processed	
Australia	77	8	--	--	20	26	37	--	--	--	--	**168**
Brazil	--	63	64	--	--	--	--	--	--	--	--	**127**
Canada	131	32	92	72	75	11	--	166	14	42	29	**664**
Chile	6	--	23	--	--	--	--	38	10	75	--	**152**
Costa Rica	12	--	--	--	--	--	--	--	--	--	--	**12**
Denmark	--	--	24	9	--	--	--	--	--	--	--	**33**
Finland	--	--	3	--	--	--	--	--	--	--	--	**3**
France	--	--	v	2	--	--	--	--	--	--	--	**2**
Germany	--	--	--	12	--	--	--	--	--	--	--	**12**
Iceland	--	--	--	--	--	48	--	--	--	--	--	**48**
Ireland	89	--	14	--	--	--	--	--	--	--	--	**103**
Israel	--	--	--	--	--	--	--	--	14	--	71	**85**
Italy	--	--	--	11	--	--	--	--	--	--	--	**11**
Japan	37	--	--	--	--	--	--	--	--	--	--	**37**
Korea, Republic Of	--	--	--	--	--	--	--	--	1	--	--	**1**
Lithuania	5	12	--	18	--	--	--	--	--	--	--	**35**

Table 13. FY 2016 Number of Import Residue Samples Analyzed, by Exporting Country and Production Type (*Cont.*)

Country	Production Type											
	Beef		Pork		Veal	Lamb Mutton	Goat	Chicken		Turkey		Total
	Fresh	Processed	Fresh	Processed	Fresh	Fresh	Fresh	Fresh	Processed	Fresh	Processed	
Mexico	152	6	16	3	--	--	5	--	4	--	9	**195**
Netherlands	--	--	12	--	4	--	--	--	--	--	--	**16**
New Zealand	24	12	--	--	38	19	18	--	--	--	--	**111**
Nicaragua	134	--	--	--	--	--	--	--	--	--	--	**134**
Northern Ireland	--	--	15	--	--	--	--	--	--	--	--	**15**
Poland	--	--	16	11	--	--	--	--	--	--	--	**27**
Spain	--	--	47	2	--	--	--	--	--	--	--	**49**
United Kingdom	--	--	58	--	--	--	--	--	--	--	--	**58**
Uruguay	542	35	--	--	1	--	--	--	--	--	--	**578**
Total	**1,209**	**168**	**384**	**140**	**138**	**104**	**60**	**204**	**43**	**117**	**109**	**2,676**

Data Source: FSIS Data Warehouse and PHIS databases.

Table 14. FY 2016 Number of Chemical Analytes Tested Per Exporting Country and Production Type

Country	Production Type											
	Beef		Pork		Veal	Lamb Mutton	Goat	Chicken		Turkey		Total
	Fresh	Processed	Fresh	Processed	Fresh	Fresh	Fresh	Fresh	Processed	Fresh	Processed	
Australia	4,449	60	--	--	1,412	2,235	3,249	--	--	--	--	**11,405**
Brazil	--	366	5,123	--	--	--	--	--	--	--	--	**5,489**
Canada	8,662	174	7,695	414	5,973	844	--	11,974	63	3,337	161	**39,297**
Chile	399	--	2,124	--	--	--	--	2,955	11	6,185	--	**11,674**
Costa Rica	650	--	--	--	--	--	--	--	--	--	--	**650**
Denmark	--	--	1,910	56	--	--	--	--	--	--	--	**1,966**
Finland	--	--	315	--	--	--	--	--	--	--	--	**315**
France	--	--	--	12	--	--	--	--	--	--	--	**12**
Germany	--	--	--	78	--	--	--	--	--	--	--	**78**
Iceland	--	--	--	--	--	3,894	--	--	--	--	--	**3,894**
Ireland	5,218	--	1,161	--	--	--	--	--	--	--	--	**6,379**
Israel	--	--	--	--	--	--	--	--	78	--	132	**210**
Italy	--	--	--	63	--	--	--	--	--	--	--	**63**
Japan	2,224	--	--		--	--	--	--	--	--	--	**2,224**
Korea, Republic Of	--	--	--	--	--	--	--	--	1	--	--	**1**
Lithuania	320	96	--	145	--	--	--	--	--	--	--	**561**

Table 14. FY 2016 Number of Chemical Analyates Tested Per Exporting Countries and Production Type (*Cont.*)

Country	Production Class											
	Beef		Pork		Veal	Lamb Mutton	Goat	Chicken		Turkey		Total
	Fresh	Processed	Fresh	Processed	Fresh	Fresh	Fresh	Fresh	Processed	Fresh	Processed	
Mexico	9,262	30	1,314	23	--	--	384	--	20	--	25	**11,058**
Netherlands	--	--	1,129	--	293	--	--	--	--	--	--	**1,422**
New Zealand	1,521	62	--	--	2,658	1,740	1,652	--	--	--	--	**7,633**
Nicaragua	9,369	--	--	--	--	--	--	--	--	--	--	**9,369**
Northern Ireland	--	--	1,438	--	--	--	--	--	--	--	--	**1,438**
Poland	--	--	1,331	61	--	--	--	--	--	--	--	**1,392**
Spain	--	--	3,820	12	--	--	--	--	--	--	--	**3,832**
United Kingdom	--	--	4,956	--	--	--	--	--	--	--	--	**4,956**
Uruguay	43,907	177	--	--	88	--	--	--	--	--	--	**44,172**
Total	**85,981**	**965**	**32,316**	**864**	**10,424**	**8,713**	**5,285**	**14,929**	**173**	**9,522**	**318**	**169,490**

Note: Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).
Data Source: FSIS Data Warehouse and PHIS databases.

Table 15. FY 2016 Number of Samples and Chemical Residues under the Import Residue Sample Program, by Exporting Country

Country	Number of Samples	Samples with Detected Non-Violative	Samples with Residue Detected Violative	Chemical Residues Analysis*
Australia	168	--	--	11,405
Brazil	127	8	--	5,489
Canada	664	1	--	39,297
Chile	152	--	--	11,674
Costa Rica	12	--	--	650
Denmark	33	--	--	1,966
Finland	3	--	--	315
France	2	--	--	12
Germany	12	--	--	78
Iceland	48	--	--	3,894
Ireland	103	--	--	6,379
Israel	85	--	--	210
Italy	11	--	--	63
Japan	37	--	--	2,224
Korea, Republic Of	1	--	--	1
Lithuania	35	--	--	561
Mexico	195	2	--	11,058
Netherlands	16	--	--	1,422
New Zealand	111	--	--	7,633
Nicaragua	134	--	2	9,368
Northern Ireland	15	--	--	1,438
Poland	27	--	--	1,392
Spain	49	--	--	3,832
United Kingdom	58	--	--	4,956
Uruguay	578	1	20	44,172
TOTAL	2,676	12	22	169,490

Note: * Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).
Data Source: FSIS Data Warehouse and PHIS databases.

Table 16. FY 2016 Import Residue Sample Program (Non-Violative and Violative) Results, by Exporting Countries, Chemical Residues and Production Class

Country	Chemical Residue	Veal	Beef	
		Residue Detected Non-Violative	Residue Detected Non-Violative	Residue Detected Violative
Brazil	Doramectin	--	1	--
	Ivermectin	--	7	--
Canada	Sulfamethazine	**1**	--	--
Mexico	Ivermectin	--	1	--
	Levamisole	--	1	--
Nicaragua	Ethion	--	--	**2**
Uruguay	Diazinon	--	--	**1**
	Ethion	--	--	**19**
	Ivermectin	--	1	--
	Total	**1**	**11**	**22**

Note: Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).**Data Source:** FSIS Data Warehouse and PHIS databases.

Appendix I

NRP Non-Violative Positive and Violative Residue Samples Results

In addition to the publication of the FY2016 United States National Residue Program samples results, FSIS will post the detailed positive non-violative, and positive violative residue results associated with the NRP sampling program in a spreadsheet format on the FSIS website:

https://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-and-reports/chemistry/red-books/red-book

This sheet includes detailed information regarding samples taken by FSIS in both the "scheduled" sampling and the "inspector-generated" sampling. FSIS plans to publish this detailed results on an ongoing basis. The purpose is to provide the residue testing results, and to increase program transparency for all stakeholders. The detailed results include :sample collection and reviewed date, the project code, the animal class, tissue type, chemical residue name, concentration value, sample results (whether positive non-violative or postive violative), chemcial concentration values (if any) and the CFR reference per chemical listed in the data sheet.

Appendix II

Statistical Table

Scheduled sampling is done to provide some assurance of detection of a violation that affects a given percentage of the sample population.

Prior to FY 2012, FSIS tested 230 to 300 samples from each production class/residue compound class pairing to obtain results that were statistically meaningful. The testing sample sizes of 230 or 300 ensured FSIS a 90 percent or 95 percent probability, respectively, of detecting at least one chemical residue violation if the violation rate is equal to or greater than one percent in the population being sampled. Starting in FY 2012, FSIS stated in its residue sampling plan that the sample size selected/tested would increase to about 800 samples for each of the nine major production class tested under Tier 1.

The statistical table provides the calculated number of samples required to ensure detection of at least one violation that affects a given percentage of the sampled population. Statistically, for a binomial distribution with sample size "n" and violation rate "v" (in decimal), if v is the true violation rate in the population and n is the number of samples, the probability, p, of finding at least one violation among the n samples (assuming random sampling) is $p = 1 - (1 - v)^n$

For example, if the true violation rate is 1% the probability of detecting at least one violation with sample sizes of 230,300,390,460, and 800 are 90%, 95%, 98%, 99%,and 99.97% respectively.

In the table below the probability of detecting at least one violation with a sample size of 800 is italicized and bolded.

Statistical Table – 2016 U.S. National Residue Program

Percentage % Violative in the population (v)	Number of samples required to detect at least one violation in (n) samples with a probability (p)				
	0.90	0.95	0.98	0.99	0.9997
	Sample Size required "n"				
10	22	29	37	44	77
5	45	59	76	90	158
1	230	300	389	459	***807***
0.57	403	525	684	***806***	1,419
0.50	460	598	***780***	919	1,618
0.37	620	***808***	1,055	1,242	2,188
0.29	***793***	1,032	1,347	1,586	2,793
0.10	2,302	2,995	3,910	4,603	8,108

The procedure to calculate the required sample size needed:

$p = 1 - (1 - v)^n$ ← Probability of detecting at least one violation in n sample of binomial distribution with violation rate v

$1 - p = (1 - v)^n$ ← Subtract one from both side of the equation. This gives the probability of detecting No violations in n samples

$\log(1 - p) = \log(1 - v)^n$ ← Apply logarithmic function to both side of the equation

$\log(1 - p) = n * \log(1 - v)$ ← A logarithmic function property

$n = \frac{\log(1 - p)}{\log(1 - v)}$ ← Sample size based on violation rate (v) and probability of detecting (p)

Appendix III

List of Chemical Residues by Class/Method

i. Veterinary Drugs

For 2016 domestic sampling, FSIS has scheduled the following classes of veterinary drug analytes:

Multi-residue method

2-Aminosulfone Albendazole	DCCD	Gamithromycin	Oxytetracycline	Sulfamethoxypyridazine
2-Amino-Flubendazole	Desethylene Ciprofloxacin	Haloperidol	Penicillin G	Sulfanitran
2-Quinoxaline Carboxylic Acid (QCA)	Diclofenac	Ipronidazole	Phenylbutazone	Sulfapyridine
Abamectin	Dicloxacillin	Ipronidazole - OH	Pirlimycin	Sulfaquinoxaline
Acepromazine	Difloxacin	Ketamine	Prednisone	Sulfathiazole
Albendazole	Dimetridazole	Ketoprofen	Ractopamine	Tetracycline
Amoxicillin	Dimetridazole - OH	Levamisole	Ronidazole	Thiabendazole
Ampicillin	Dipyrone	Lincomycin	Salbutamol	Tildipirosin
Azaperone	Doramectin	Melengestrol Acetate	Sarafloxacin	Tilmicosin
Butorphanol	Doxycycline	Meloxicam	Selamectin	Tolfenamic Acid
Carazolol	Emamectin Benzoate	Metronidazole	Sulfachloropyridazine	Tulathromycin A
Cefazolin	Enrofloxacin	– Metronidazole-OH	Sulfadiazine	Tylosin
Chloramphenicol	Eprinomectin	Morantel tartrate	Sulfadimethoxine	Tyvalosin
Chlortetracycline	Erythromycin A	Moxidectin	Sulfadoxine	Virginiamycin
Cimaterol	Fenbendazole	Nafcillin	Sulfaethoxypyridazine	Xylazine
Ciprofloxacin	Fenbendazole sulphone	Norfloxacin	Sulfamerazine	Zeranol (β-Zearalanol)
Clindamycin	Florfenicol	Orbifloxacin	Sulfamethazine	
Cloxacillin	Flubendazole	Oxacillin	Sulfamethizole	
Danofloxacin	Flunixin	Oxyphenylbutazone	Sulfamethoxazole	

Aminoglycoside Method

Amikacin	Gentamicin	Neomycin
Apramycin	Hygromycin B	Spectinomycin
Dihydrostreptomycin	Kanamycin	Streptomycin

Hormones Method

Megestrol	Melengestrol Acetate	Hexestrol	Zeranol

Beta-Agonist Method

Cimaterol	Ractopamine	Zilpaterol
Clenbuterol	Salbutamol	

Avermectin Method

Doramectin	Ivermectin	Moxidectin

Nitrofuran Method

3-Amino-2-oxazolidinone (AOZ)	1-Aminohydantoin (AHD)	Semicarbazide (SEM)
3-Amino-5-morpholinomethyl-2-oxazolidinone (AMOZ)		

Carbadox Method
Quinoxaline-2-carboxylic acid

ii. Pesticides and environmental contaminants

a. Pesticide Method

1-Naphthol	Coumaphos O	Fluroxypyr-1-Methylhepyl-Ester	Pentachlorobenzene (PCB)
3-Hydroxycarbofuran	Coumaphos S	Fluvalinate	Permethrin (cis&trans)
Acephate	DDD o,p’	Heptachlor	Piperonyl butoxide
Acetamiprid	DDD p,p’ + DDT, o,p'	Heptachlor epoxide (cis+ trans) or (B+A)	Pirimiphos methyl
Alachlor	DDE o,p’	Hexachlorobenzene (HCB)	Prallethrin
Aldicarb	DDE p,p’	Hexazinone	Profenofos
Aldicarb sulfone	DDT p,p’	Hexythiazox	Pronamide
Aldicarb sulfoxide	Deethylatrazine	Imazalil	Propachlor
Aldrin	Diazinon	Imidacloprid	Propanil
Atrazine	Dichlorvos (DDVP)	Indoxacarb	Propetamphos
Azinphos methyl	Dieldrin	Lindane (BHC gamma)	Propiconazole
Azoxystrobin	Difenoconazole	Linuron	Pyraclostrobin
Benoxacor	Diflubenzuron	Malathion	Pyrethrin I
Bifenthrin	Dimethoate	Metalaxyl	Pyrethrin II
Boscalid	Diuron	Methamidophos	Pyridaben
Buprofezin	Endosulfan I	Methomyl	Pyriproxyfen
Carbaryl	Endosulfan II	Methoxyfenozide	Resmethrin (cis&trans)
Carbofuran	Endosulfan sulfate	Metolachlor	Simazine
Carfentrazone ethyl	Ethion	Metribuzin	Sulprofos
Chlordane cis	Ethion monoxon	MGK-264 (isomers 1 & 2)	Tebufenozide

Chlordane trans	Ethofumesate	Myclobutanil	Tefluthrin
Chloroneb	Fenoxaprop ethyl	Nonachlor cis	Tetrachlorvinphos
Chlorothalonil	Fenpropathrin	Nonachlor trans	Tetraconazole
Chlorpropham	Fipronil	Norflurazon	Thiabendazole
Chlorpyrifos	Fipronil desulfinyl	Omethoate	Thiamethoxam
Chlorpyrifos methyl	Fipronil sulfide	Oxychlordane	Thiobencarb
Clothianidin	Fluridone	Pentachloroaniline (PCA)	Trifloxystrobin
1-Naphthol	Coumaphos O	Fluroxypyr-1-Methylhepyl-Ester	Pentachlorobenzene (PCB)
3-Hydroxycarbofuran	Coumaphos S	Fluvalinate	Permethrin (cis&trans)
Acephate	DDD o,p’	Heptachlor	Piperonyl butoxide
Acetamiprid	DDD p,p’ + DDT, o,p'	Heptachlor epoxide (cis+ trans) or (B+A)	Pirimiphos methyl
Alachlor	DDE o,p’	Hexachlorobenzene (HCB)	Prallethrin
Aldicarb	DDE p,p’	Hexazinone	Profenofos
Aldicarb sulfone	DDT p,p’	Hexythiazox	Pronamide
Aldicarb sulfoxide	Deethylatrazine	Imazalil	Propachlor
Aldrin	Diazinon	Imidacloprid	Propanil
Atrazine	Dichlorvos (DDVP)	Indoxacarb	Propetamphos
Azinphos methyl	Dieldrin	Lindane (BHC gamma)	Propiconazole
Azoxystrobin	Difenoconazole	Linuron	Pyraclostrobin
Benoxacor	Diflubenzuron	Malathion	Pyrethrin I
Bifenthrin	Dimethoate	Metalaxyl	Pyrethrin II
Boscalid	Diuron	Methamidophos	Pyridaben
Buprofezin	Endosulfan I	Methomyl	Pyriproxyfen
Carbaryl	Endosulfan II	Methoxyfenozide	Resmethrin (cis&trans)
Carbofuran	Endosulfan sulfate	Metolachlor	Simazine
Carfentrazone ethyl	Ethion	Metribuzin	Sulprofos
Chlordane cis	Ethion monoxon	MGK-264 (isomers 1 & 2)	Tebufenozide
Chlordane trans	Ethofumesate	Myclobutanil	Tefluthrin
Chloroneb	Fenoxaprop ethyl	Nonachlor cis	Tetrachlorvinphos
Chlorothalonil	Fenpropathrin	Nonachlor trans	Tetraconazole
Chlorpropham	Fipronil	Norflurazon	Thiabendazole
Chlorpyrifos	Fipronil desulfinyl	Omethoate	Thiamethoxam

Chlorpyrifos methyl	Fipronil sulfide	Oxychlordane	Thiobencarb
Clothianidin	Fluridone	Pentachloroaniline (PCA)	Trifloxystrobin

b. Metals Method

Aluminum (Al)	Copper (Cu)	Selenium (Se)
Barium (Ba)	Iron (Fe)	Strontium (Sr)
Boron (B)	Lead (Pb)	Thallium (Tl)
Cadmium (Cd)	Manganese (Mn)	Vanadium (V)
Chromium (Cr)	Molybdenum (Mo)	Zinc (Zn)
Cobalt (Co)	Nickel (Ni)	

Appendix IV

U.S. NRP – Domestic Scheduled Sampling Program

Year	Number of Samples	Number of Violative Samples	Number of Non-Violative Positive Analytes	Number of Violative Chemical Residues
* FY2013	4,583	19	23	8
FY2014	6,066	10	34	10
FY2015	6,445	12	23	8
FY2016	7,067	26	24	11

* **Note:** FSIS moved to a fiscal evaluation period beginning with FY12. FY 2013 covers only Jan-Sept, 2013.

Appendix V

U.S. NRP – Import Re-inspection Sampling Program

Year	Number of Samples	Number of Violative Samples	Violative Residues
* FY2013	817	4	Avermectins
FY2014	1,967	8	Ivermectin (7), Zilpaterol (1)
FY2015	2,922	7	Abamectin (1) Ethion (5), Piperonyl Butoxide (1)
FY2016	2,676	22	Ethion (21), Diazinon (1)

*** Note:** FSIS moved to a fiscal evaluation period beginning with FY12. FY 2013 covers only Jan-Sept, 2013.

Appendix VI

NRP – Domestic Inspector Generated Sampling Program (*include* KIS™ *test*) & lab confirmed residue results

Year	Number of Samples / (Include In-plant KIS™ Screens Tests)	Number of Samples Tested in FSIS Labs / (include in-plant KIS™ screens positive)	Number of Lab-Confirmed Violative Analytes / Number of Violative Carcasses	Top Three Violative Chemical Residue	Number of Lab-Confirmed Non-Violative Positive Analytes	Top Three Non-Violative Chemical Residue
***FY2013**	170,692 / (**170,560**)	4,100 / (**3,968**)	1,265 / **1,053**	Ceftiofur Penicillin Neomycin	1,099	Oxytetracyline Neomycin Ceftiofur
FY2014	210,705 / (**210,516**)	5,048 / (**4,859**)	1,408 / **1,136**	Ceftiofur Penicillin Neomycin	1,150	Oxytetracyline Tulathromycin Penicillin
FY2015	184,167 / **(184,010)**	4,179 / (**4,022**)	1,024 / **796**	Ceftiofur Penicillin Sulfamethazine	873	Tulathromycin Oxytetracyline Neomycin
FY2016	182,313 / **(182,184)**	3,778 / (**3,649**)	893 / **732**	Ceftiofur Penicillin Sulfadimethoxine	728	Oxytetracycline Tulathromycin Penicillin

Note:

- (**Number of KIS™ test samples in paranthesis**)
- Multiple violative analytes in different tissue types may be associated with a single sample (Carcass).
- FSIS moved to a fiscal evaluation period beginning w/FY13. FY 2013 covers Jan-Sept, 2013 only.

Appendix VII

2016 FSIS Residue Sampling for Siluriformes

On December 2, 2015, FSIS published the final rule, "Mandatory Inspection of Fish of the Order Siluriformes and Products Derived From Such Fish." The 2008 Farm Bill amended the Federal Meat Inspection Act (FMIA), to make Siluriformes a species amendable to the FMIA and therefore, subject to FSIS inspection. FSIS is providing an 18 month transitional period for the inspection of Siluriformes and the residue testing will be done based on parameters set forth in the final rule. During the first 18 months, FSIS will schedule routine testing of Siluriformes for dyes (malachite green and gentian violet), nitrofurans, veterinary drugs, metals, and pesticides residues.

Note: The sampling scheme may change during the 18 month transitional period based on sampling results and findings by FSIS.

	Domestic	Imports	Total
Siluriformes	**77**	**84**	**161**

Siluriformes	Chemical Class May 2015- Sep 2016				
	Dyes	Metals	MRM	Nitrofurans	Pesticides
Domestic	√	√	√	√	√
Imports	√	√	√	√	√

Table 17. FY2016 NRP Residue Scheduled Samples -Number of Residue Samples Tested Per Chemical Method by Sampling Plan

Siluriformes (# Samples Collected)		Number of Samples per Chemical Method				
		Dyes	Metals	MRM	Nitrofurans	Pesticides
Domestic	**(77)**	31 **(1)**	31	77	46	46
Import	**(84)**	42	42	42 **(1)**	42 **(1)**	42
Total	**(161)**	**73**	**73**	**119**	**88**	**88**

Note: Number of violative samples **(in parenthesis)**
Data Source: FSIS Data Warehouse and PHIS databases.

Table 18. FY 2016 NRP Residue Scheduled Samples - Number of Chemical Analytes Tested Per Chemical Method by Sampling Plan

Siluriformes (# Samples Collected)	Number of Chemical Analytes per Chemical Method					
	Dyes	Metals	MRM	Nitrofurans	Pesticides	Total
Domestic (77)	154	821	14,283	230	7,338	22,826
Import (84)	203	1181	8,105	210	6,274	15,973
Total (161)	**357**	**2,002**	**22,388**	**440**	**13,612**	**38,799**

Note: Multiple analytes may be associated with the same sample. Not all samples are tested for all chemical method. Number of samples per chemical method is indicated in Table 4

Data Source: FSIS Data Warehouse and PHIS databases.

Table 19. FY 2016 NRP Siluriformes Residue Inspection Program Violations

Animal	Sampling	Compound	Concentration	Units	Tolerance Level Value	Authority (CFR Citation)
Siluriformes	Domestic	Crystal Violet	0.162	ppm		
Siluriformes	Import	Enrofloxacin	22.500	ppm		
Siluriformes	Import	Gentian Violet	16.1	ppb		

Appendix 6

WARNING LETTER

Yippee Farms, LLC

MARCS-CMS 628623 — MAY 05, 2022

Delivery Method:

VIA UPS

Product:

Animal & Veterinary
Food & Beverages

Recipient:

Arlin L. Benner

Owner

Yippee Farms, LLC

1020 Pinkerton Road
Mount Joy, PA 17552-9242
United States

Issuing Office:

Division of Human and Animal Food Operations East II

United States

May 5, 2022

CMS #628623
WARNING LETTER

Dear Mr. Benner,

An inspection of your dairy operation located at 1103 Iron Bridge Road, Mount Joy, Pennsylvania, was conducted by representatives of the U.S. Food and Drug Administration

Appendix 6

(FDA) on December 8 and 10, 2021. This letter notifies you of violations of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) that were revealed during our inspection of your operation and noted upon further review of the information collected during the inspection. You can find the FD&C Act and its associated regulations on the internet through links on the FDA's web page at www.fda.gov. (//www.fda.gov.) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)

Our investigation found your firm responsible for causing drug residues of meloxicam and sulfadimethoxine in the kidney tissue of bob veal calf **(b)(6)**. Specifically, on March 4, 2021, you sold this bob veal calf for slaughter as food. The animal was slaughtered on or about March 5, 2021, at **(b)(4)**. The USDA/FSIS analysis of tissue samples collected from this animal identified the presence of meloxicam and sulfadimethoxine in the kidney tissue. FDA has not established a tolerance for residues of meloxicam and sulfadimethoxine, in uncooked edible tissues of this bovine animal class.

At the close of the inspection, you were issued a Form FDA 483, Inspectional Observations (FDA 483). We have not received a response, from you, to the FDA 483 as of the date on this letter.

Adulteration of Animals Offered for Human Consumption

Our investigation found that you hold animals under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. Specifically, you failed to maintain complete treatment records for a bob veal calf with farm tag **(b)(6)** when your employee did not record the administration of meloxicam and sulfadimethoxine on the pen treatment record for this animal. Due to the incomplete treatment records, the calf with farm tag **(b)(6)** was sold for slaughter before the proper meat withdrawal time indicated on the prescription label for the human drug meloxicam. Additionally, your treatment records, in general, do not identify the condition being treated for your medicated heifer calves. Food from animals held under such conditions is adulterated within the meaning of section 402(a)(4) of the FD&C Act [21 U.S.C. § 342(a)(4)].

Adulteration of New Animal Drugs

Our inspection also revealed that you adulterated the human drug meloxicam (NDC **(b)(4)**) and the drug **(b)(4)** (sulfadimethoxine, NADA **(b)(4)**) because you failed to use the drugs in conformance with their approved labeling ("extralabel use"). Extralabel use is only permitted if the use complies with sections 512(a)(4) and 512(a)(5) of the FD&C Act [21 U.S.C. 360b(a)(4) and 360b(a)(5)], and with Title 21, Code of Federal Regulations, Part 530 (21 CFR Part 530), including that the use is by or on the lawful order of a licensed veterinarian within the context of a valid veterinarian/client/patient relationship as defined by 21 CFR 530.3(i)(1). Our investigation found that your extralabel use of meloxicam and **(b)(4)**, however, failed to

Appendix 6

comply with these requirements.

Specifically:

• Around March 3, 2021, your employee treated a bob veal calf identified with farm tag **(b)(6)** with meloxicam and **(b)(4)** (sulfadimethoxine) for scours. Additionally, you stated that you routinely administer meloxicam for scours. However, the veterinary prescription label stated that meloxicam was prescribed to only treat pain in calves due to dehorning. Your use of the drug for scours was therefore an extralabel use.
• You administered meloxicam to bob veal calf identified with farm tag **(b)(4)** in an extralabel manner by not following the withdrawal period set forth in the veterinary prescription label, which is **(b)(4)**. You stated that an employee medicated this animal with meloxicam at an unknown date prior to the calf being sold. This calf was only **(b)(4)** old when slaughtered for food; therefore, the calf could not have been held for the required withdrawal time of **(b)(4)**.
• You administered **(b)(4)** (sulfadimethoxine) in an extralabel manner by treating a preruminant bob veal calf identified with farm tag **(b)(6)** for scours. The approved labeling of **(b)(4)** (sulfadimethoxine) **(b)(4)** states in part, "**(b)(4)**".

Your extralabel use of meloxicam and **(b)(4)** (sulfadimethoxine) were not under the supervision of a licensed veterinarian, in violation of 21 C.F.R. 530.11(a).

Because your extralabel use of these drugs was not in compliance with 21 CFR Part 530, you caused the drugs to be unsafe under sections 512(a)(4) and 512 (a)(5) of the Act [21 U.S.C. § 360b(a)(4)(A)] and adulterated under section 501(a)(5) of the Act [21 U.S.C. § 351(a)(5)].

Conclusion

This letter is not intended to be an all-inclusive statement of violations that may exist at your facility. As a producer of animals offered for use as food, you are responsible for ensuring that your overall operation and the food you distribute is in compliance with the law, and that your firm complies with all requirements of federal law and FDA regulations.

This letter notifies you of our concerns and provides you an opportunity to address them. You should take prompt action to correct the violations described in this letter and to establish procedures to ensure that these violations do not recur. Failure to adequately address this matter may lead to legal or regulatory action without further notice, including without limitation, seizure and/or injunction.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct any violations and include copies of any available documentation demonstrating that corrections have been made. If you cannot

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complete corrective actions within fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction. If you believe that you have complied with the FD&C Act and FDA regulations, include your reasoning and any supporting information for our consideration.

Your written response should be sent to Compliance Officer Andrew J. Howard at United States Food & Drug Administration, 11155 Dolfield Blvd, Suite 117, Owings Mills, MD 21117. An emailed response is also acceptable. Files greater than 100 megabytes may be submitted as smaller files in separate emails. If you have questions regarding this letter, please contact CO Howard by telephone at (410) 779-5125, or by email at Andrew.Howard@fda.hhs.gov.

Sincerely,
/S/

Randy F. Pack
District Director/Program Division Director
Baltimore District Office
Human & Animal Food East, Division 2
Office of Regulatory Affairs
U.S. Food and Drug Administration
randy.pack@fda.hhs.gov

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-action

Appendix 7

National Library of Medicine
National Center for Biotechnology Information

DATA SOURCES > HAZARDOUS SUBSTANCES DATA BANK (HSDB) > ANNOTATION RECORD

Meloxicam

Hazardous Substances DataBank Number	7741
Related PubChem Records	Related CIDs 54677470

1 Human Health Effects

1.1 Human Toxicity Excerpts (Complete)

/HUMAN EXPOSURE STUDIES/ This study aimed to assess the effect of meloxicam on female ovulation. Twenty consented fertile females were monitored for 4 menstrual cycles: a baseline cycle, 2 treatment cycles, and a washout cycle between treatment cycles. In the first cycle visit, transvaginal ultrasound was performed, a blood sample for progesterone and meloxicam analysis was withdrawn, and volunteers were given a luteinizing hormone (LH) urine test kit and meloxicam or placebo. Volunteers started the treatment on the following day and asked to return the day the LH kit was positive to detect the dominant follicle. At subsequent visits, transvaginal ultrasound and progesterone and meloxicam levels were investigated. Compared to placebo, a 5-day delay in follicle rupture, a 55.7% increase in the mean maximum follicle diameter, and 33.5% decrease of plasma progesterone level were observed in the meloxicam-treated group. Such demonstrated meloxicam effects were reversed in participants who were randomized to meloxicam first and then placebo. Only minor side effects were reported by volunteers during the course of treatment. It is concluded that meloxicam resulted in a reversible delay of ovulation, an increase in follicular diameter, and a decrease in plasma progesterone level.

PMID:16855077

Bata MS et al; J Clin Pharmacol 46 (8): 925-32 (2006).

/SIGNS AND SYMPTOMS/ Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/SIGNS AND SYMPTOMS/ Borderline elevations of one or more liver function tests may occur in up to 15% of patients treated with NSAIAs, including meloxicam; meaningful (3 times the upper limit of normal) elevations of serum ALT (SGT) or AST (SGOT) reported in approximately 1% of patients receiving other NSAIAs. Severe, sometimes fatal, reactions (eg, jaundice, fulminant hepatitis, liver necrosis, hepatic failure) reported rarely in patients receiving NSAIAs. Discontinue use if clinical signs and symptoms occur.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

/CASE REPORTS/ ... /Investigators/ describe a patient who presented with bloody diarrhea after 15 mg meloxicam daily for 10 days for osteoarthritis. The endoscopic and histological features were consistent with the diagnosis of ischemic colitis. Symptoms and endoscopic lesions quickly regressed within 1 week of meloxicam withdrawal. There was no evidence of another cause of colonic ischemia. ...

PMID:11247558

Garcia B et al; Lancet 357 (9257): 690 (2001).

/CASE REPORTS/ /The authors/ report the case of a female patient with rheumatoid arthritis who developed acute cytolytic hepatitis due to meloxicam. ... The acute cytolytic hepatitis occurred rapidly after meloxicam administration and was associated with the development of antinuclear antibodies suggesting a hypersensitivity mechanism. ...

PMID:10427794

Staerkel P, Horsmans Y; Acta Gastroenterol Belg 62 (2): 255-6 (1999).

/CASE REPORTS/ A 47-year-old woman presented with a 1-week history of spontaneous prominent and painful bruising and hematomata, 5-6 weeks after commencing meloxicam 15 mg daily for osteoarthritis and plantar fasciitis. The bruises varied in size from 2 cm x 2 cm to 3 cm x 4 cm. She had a past history of acne rosacea, for which she was taking clonidine 100 ug daily, and reflux esophagitis, for which she was taking pantoprazole 40 mg daily. Meloxicam, being the only new drug taken by the patient, was suspected as the causative agent and was therefore discontinued. Activated partial thromboplastin time

(APTT) at presentation was 58 s (reference range, 22 s -38 s). A week after stopping meloxicam, it had fallen to 37 s. All other hematological parameters, including platelet count and international normalized ratio, were normal, as were renal and liver function. New bruises and hematomata stopped appearing 2 days after the patient stopped taking meloxicam. She continued taking clonidine and pantoprazole. ... In spite of these contrary findings, the prolongation of APTT and spontaneous bruising and hematomata in this patient were /believed to be/ directly attributable to meloxicam, as the bruises disappeared 2-3 days after stopping the drug (with no other changes in the patient's existing medication) and a repeat APTT a week after cessation of the drug was normal.

PMID:16097928

Kurien AM; Med J Aust 183 (4): 219 (2005).

/CASE REPORTS/ ... /Investigators/ report 2 cases of meloxicam-induced anaphylactic reaction with no sensitivity to another selective cyclooxygenase 2 inhibitor. ...

PMID:17039673

Bavbek S et al; J Investig Allergol Clin Immunol 16 (5): 317-20 (2006).

/EPIDEMIOLOGY STUDIES/ This article provides a systematic review of the frequency and severity of adverse gastrointestinal (GI) events among patients using meloxicam, a cyclooxygenase (COX)-2-selective nonsteroidal anti-inflammatory drug (NSAID). A MEDLINE search of English language articles from 1990-1998, a manual search of citations from primary trials and review articles, and a manual search of proceedings from international gastroenterology meetings were conducted. Randomized clinical trials comparing the frequency of GI adverse events for meloxicam versus non-COX-2-selective NSAIDs were selected. Specific data about the frequency of dyspepsia; perforations, ulcers, and bleeds (PUBs); and withdrawal of medication because of adverse GI events was also extracted. From a pool of 62 potentially relevant citations, 12 randomized trials were identified. All trials concerning symptomatic GI adverse events used the World Health Organization's Adverse Reaction Terminology List (WHO-ARTL) to code adverse events. Patients using meloxicam had fewer GI adverse events compared with non-COX-2-selective NSAIDs (odds ratio = 0.64; 95% confidence interval [CI], 0.59-0.69). Patients using meloxicam experienced less dyspepsia (odds ratio = 0.73; 95% CI, 0.64-0.84), fewer PUBs (odds ratio = 0.52; 95% CI, 0.28-0.96), and less frequent discontinuation of NSAID because of adverse GI events (odds ratio = 0.59; 95% CI, 0.52-0.67) compared with non-COX-2 selective NSAIDs. Meloxicam, a COX-2-selective NSAID, appears to cause fewer adverse GI events than standard, non-COX-2-selective NSAIDs. ...

PMID:10628593

Schoenfeld P; Am J Med 107 (6A): 48S-54S (1999).

/EPIDEMIOLOGY STUDIES/ The aims of the study were to: determine the rate of adverse events associated with meloxicam in general practice, stratify these rates by selected risk

factors, and to identify signals of previously unsuspected adverse events associated with meloxicam. As part of the national prescription-event monitoring pharmacovigilance system for newly launched drugs in general practice, all patients prescribed meloxicam in England between December 1996 and March 1997 were identified by the central Prescription Pricing Authority. /Investigators/ sent short questionnaires to all prescribers asking about adverse events experienced within 6 months of the first prescription. There were 19,087 patients in the study. The rate of dyspepsia during the first month of exposure was 28.3 per 1000 patient-months. There were 33 reports of upper gastrointestinal hemorrhage during treatment (rate: 0.4 per 1000 months). A history of gastrointestinal disorder in the previous year was associated with an increased rate of dyspepsia (rate ratio: 3.0; 95% confidence interval: 2.6, 3.4), abdominal pain (2.1; 1.6, 2.6), and peptic ulcer (4.0; 1.4, 13.2). Prior NSAID use was associated with a 20-30% decrease in the rate of dyspepsia and abdominal pain in patients starting meloxicam, while patients prescribed concomitant gastroprotective agents had a two to three-fold increased rate of dyspepsia, abdominal pain and peptic ulceration. Other rare events were thrombocytopenia (n = 2); interstitial nephritis (n = 1) and idiosyncratic liver abnormalities (n = 1). ...

PMID:10886116

Full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2014964

Martin RM et al; Br J Clin Pharmacol 50 (1): 35-42 (2000).

/EPIDEMIOLOGY STUDIES/ To assess the risk of serious gastrointestinal and thromboembolic complications with approved doses of meloxicam. /Investigators/ pooled data from clinical trials of meloxicam at doses of 7.5 or 15 mg/d. A blinded gastrointestinal adjudication committee used prespecified criteria to identify gastric or duodenal perforation, gastric outlet obstruction, or hemodynamically important upper gastrointestinal bleeding. For analysis of thromboembolic complications, investigator-reported events were analyzed without adjudication. /The authors/ analyzed data from 24,196 patients from 28 trials, most of whom had been followed for up to 60 days. Of these patients, 13,118 received meloxicam (10,158 received a daily dose of 7.5 mg and 2960 received 15 mg), 5283 were treated with diclofenac 100 mg, 181 received diclofenac 150 mg, 5371 were treated with piroxicam 20 mg, and 243 received naproxen 500 mg twice daily. Patients who received 7.5 mg of meloxicam daily had a 0.03% risk of serious upper gastrointestinal events, which was significantly lower than the risk in those who received diclofenac, naproxen, or piroxicam (P <0.02). With the 15 mg daily dose of meloxicam, this risk was significantly different only when compared with piroxicam (P = 0.03). The risk of thromboembolic events in patients treated with meloxicam at either dose was lower than with diclofenac, but similar to that observed with piroxicam and naproxen. ...

PMID:15234645

Singh G et al; Am J Med 117 (2): 100-6 (2004).

Appendix 7

/EPIDEMIOLOGY STUDIES/ ... To investigate the risk of /congestive heart failure/ (CHF) associated with combined use of diuretics and NSAIDs in patients older than 55 years. /The authors/ conducted a study in a base cohort of 10,519 recipients of diuretics and NSAIDs identified in the PHARMO database during the period from 1986 through 1992. The incidence density of hospitalizations for CHF during exposure to both diuretics and NSAIDs (index) was compared with that during exposure to diuretics only (reference). /Investigators/ found an overall increased risk of hospitalization for CHF during periods of concomitant use of diuretics and NSAIDs compared with use of diuretics only (crude relative risk, 2.2; 95% confidence interval, 1.7-2.9). After adjusting for cofactors including age, sex, history of hospitalization, and drug use, a 2-fold increased risk remained (relative risk, 1.8; 95% confidence interval, 1.4-2.4). Use of NSAIDs in elderly patients taking diuretics is associated with a 2-fold increased risk of hospitalization for CHF, especially in those with existing serious CHF.

PMID:9605782

Heerdink ER et al; Arch Intern Med 158 (10): 1108-12 (1998).

/EPIDEMIOLOGY STUDIES/ Using national data (2001-2003), this study explored the risk of acute myocardial infarction (AMI), angina, stroke and transient ischemic attack (TIA) in long-term users of rofecoxib and celecoxib in Taiwan and compared this data with that for those using meloxicam. Patients included in the study had used celecoxib, rofecoxib or meloxicam for at least 180 days. Data were taken from National Health Insurance database for the period from 2001 to 2003. Main outcome measurements were the occurrence of AMI, angina, stroke or TIA after the initiation of long-term continuous use of these drugs. Person-time exposures and hazard ratios (HRs) were calculated based on data from 9602 eligible patients. In patients without a history of a cardiovascular event within the year before drug treatment began, the overall rates of AMI, angina, stroke and TIA were 1.1%, 0.6%, 2.0% and 0.6%, respectively. In those with cardiovascular events in the year before treatment began, the overall rates of AMI, angina, stroke and TIA were 5.0%, 4.8%, 6.6% and 5.8%, respectively. Compared with meloxicam users, celecoxib users had lower HRs for the development of AMI (HR 0.78, 95% CI 0.63, 0.96) and stroke (HR 0.81, 95% CI 0.70, 0.93). Rofecoxib users were at no higher risk of cardiovascular events than those receiving meloxicam. Regardless of treatment, having had a cardiovascular event in the year before treatment began played a significant role in the development of the same cardiovascular event during the prescription period; the HRs associated with having had the same cardiovascular event in the past year, versus not having had such an event, were 3.02 (95% CI 1.44, 6.32) for AMI, 5.82 (95% CI 3.19, 10.63) for angina, 2.44 (95% CI 1.79, 3.33) for stroke and 7.16 (95% CI 3.70, 13.87) for TIA. ...

PMID:16524325

Huang WF et al; Drug Saf 29 (3): 261-72 (2006).

/GENOTOXICITY/ Meloxicam was not ... clastogenic in ... a chromosome aberration assay with human lymphocytes.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/OTHER TOXICITY INFORMATION/ Contraindications: Known hypersensitivity to meloxicam or any ingredient in the formulation. History of urticaria, angioedema, bronchospasm, severe rhinitis, or shock precipitated by aspirin or other NSAIAs. History of aspirin triad (aspirin sensitivity, asthma, and nasal polyps). Treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

/OTHER TOXICITY INFORMATION/ Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, meloxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/OTHER TOXICITY INFORMATION/ ... Serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) can occur in patients receiving meloxicam. These serious skin reactions may occur without warning. Discontinue meloxicam at the first appearance of rash or any other sign of hypersensitivity.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

1.2 Populations at Special Risk (Complete)

Caution should be used when initiating treatment with meloxicam in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with meloxicam. Caution is also recommended in patients with pre-existing kidney disease.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

2 Emergency Medical Treatment

Appendix 7

2.1 Antidote and Emergency Treatment (Complete)

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing water. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of water for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag valve mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as albuterol for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with diazepam or lorazepam ... . Use proparacaine hydrochloride to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160-1

3 Animal Toxicity Studies

Appendix 7

3.1 Non-Human Toxicity Excerpts (Complete)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to induce gastrointestinal damage including bleeding, ulceration and perforation in humans and animals. The aim of this study was to compare the effects of two oxicams, preferential cyclooxygenase (COX)-1 or COX-2 inhibitors, on both gastric mucosa and some biological parameters (hematological, hepatic and renal) after subchronic administration (14 and 28 days) in rats. Neutrophil infiltration was also assessed. Equipotent doses of meloxicam (3.75 and 7.5 mg/kg) and piroxicam (5 and 10 mg/kg) were administered. Both drugs dose-dependently caused multiple gastric erosions and hemorrhage in rats after 14 and 28 days of administration. Treatment with meloxicam led to a higher gastric damage than with piroxicam on day 14 although these results were not significant. The levels of myeloperoxidase activity (as an index of neutrophil infiltration) were not changed compared with control after drug treatment. All the hematological parameters obtained after drugs administration for 14 and 28 days were in the range of normal values, and a significant increase in platelet levels could be observed in the group treated with 5 mg/kg of piroxicam for 14 days. Aspartate aminotransferase (AST or GOT) increased significantly after 14 days, but after 28 days the values returned to normality. Creatinine and urea did not undergo significant changes except for the piroxicam 14-day 5 mg/kg group, in which uremia increased significantly over normal values. ...

PMID:12207113

Villegas I et al; Pharmacology 66 (2): 68-75 (2002).

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day for 99 weeks.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day throughout organogenesis. An increased incidence of stillbirths was observed when rats were given oral doses greater than or equal to 1 mg/kg/day throughout organogenesis.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses greater than or equal to 0.125 mg/kg/day when rats were treated during the late gestation and lactation period

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day and embryolethality at oral doses greater than or equal to 5 mg/kg/day when rabbits were treated throughout organogenesis.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively. However, an increased incidence of embryolethality at oral doses greater than or equal to 1 mg/kg/day was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/GENOTOXICITY/ Meloxicam was not mutagenic in an Ames assay, or clastogenic in ... an in vivo micronucleus test in mouse bone marrow.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

/ALTERNATIVE and IN VITRO TESTS/ The nephrotoxicity of diclofenac, a non-steroidal anti-inflammatory drug that inhibits both isoforms of cyclooxygenase (COX) has been reported to be fatal to vultures but this was not so with meloxicam which is COX-2 selective. /This/ ...study showed that diclofenac was more toxic than meloxicam to both the proximal tubular LLC-PK1 cells and the distal tubular Madin-Darby canine kidney type II (MDCKII) cells, and that LLC-PK1 cells were more susceptible. Exposure of MDCKII cells to meloxicam caused activation of caspase-9/-3 and release of cytochrome c. These observations together with a positive annexin V-FITC staining implicate an intrinsic mitochondrial cell death pathway by apoptosis. Diclofenac-treated MDCKII cells on the other hand showed extensive propidium iodide staining, suggestive of cell death by necrosis. The mode of cell death in LLC-PK1 cells was however less well-defined with positive annexin V-FITC staining but minimal increase in caspase-3 activity alluding to a caspase-independent pathway.

PMID:18325323

Na LE et al; Biochem Biophys Res Commun 369 (3) : 873-7 (2008).

/VETERINARY CASE REPORTS/ A 4-year-old female Siberian Husky was diagnosed with pyogranulomatous steatitis at the site of a recurrence of left anal sac rupture (day 1).

Carprofen and orbifloxacin were given for 13 days without improvement. A single dose of meloxicam was administered prior to surgical resection of the anal sac, and based on elevated liver enzyme activity, liver supportive therapy was initiated. The dog received carprofen and orbifloxacin orally on the evening of day 14. The dog became anorectic the following morning, and began vomiting. Despite supportive therapy, the dog was unresponsive to treatment and died on day 16. Postmortem examination revealed severe vacuolar change and acute necrosis of hepatocytes consistent with carprofen and meloxicam induced-toxicosis.

PMID:16276063

Nakagawa K et al; J Vet Med Si 67 (10): 1051-3 (2005).

4 Metabolism / Pharmacokinetics

4.1 Metabolism / Metabolites (Complete)

Meloxicam is almost completely metabolized to four pharmacologically inactive metabolites. The major metabolite, 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism was formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). In vitro studies indicate that cytochrome P-450 2C9 plays an important role in this metabolic pathway with a minor contribution of the CYP 3A4 isozyme.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Patients' peroxidase activity is probably responsible for /two other/ metabolites which account for 16% and 4% of the administered dose, respectively.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam is extensively metabolized to inactive metabolites in the liver, principally via the cytochrome P-450 (CYP) 2C9 isoenzyme, with minor contribution by CYP3A4. The drug and its metabolites are excreted in urine and feces, and meloxicam undergoes substantial biliary secretion and enterohepatic recirculation.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2163

The metabolism of Meloxicam (ME) and the cytochrome(s) P450 (CYPs) involved were analysed by using primary human hepatocytes, human liver microsomes and microsomes from recombinant human B-lymphoblastoid cell lines. While human hepatocytes were

capable of converting ME to a 5-hydroxymethyl metabolite (M7) and then to a 5-carboxyderivative (M5), human liver microsomes formed mostly only the 5-hydroxymethylderivative. The kinetics of the formation of M7 by human liver microsomes were biphasic with Km = 13.6 +/- 9.5 and 381 +/- 55.2 uM respectively. The corresponding Vmax were 33.7 +/- 24.2 and 143 +/- 83.9 pmol/min/mg protein respectively. CYP2C9 and, to a much lesser extent, CYP3A4 were found to convert ME to M7. The involvement of 2C9 was demonstrated by inhibition of tolbutamide hydroxylase activity in the presence of ME, inhibition of ME metabolism by sulphaphenazole, correlation between ME metabolism and tolbutamide hydroxylase activity and active metabolism of ME by recombinant 2C9. The involvement of 3A4 was shown by inhibition of ME metabolism by ketoconazole, correlation between ME metabolism and nifedipine oxidase activity and metabolism of ME by recombinant 3A4. Kinetics of the formation of M7 by the individual enzymes resulted in a Km = 9.6 uM and Vmax = 8.4 pmol/min/mg protein for 2C9 and a Km = 475 uM and Vmax = 23 pmol/min/mg protein for 3A4.

PMID:9493314

Chesne C et al; Xenobiotica 28 (1): 1-13 (1998).

... The basic clinical pharmacokinetics of meloxicam (7.5-30 mg) have been investigated in 78 healthy male volunteers after single and multiple dosing via oral, intravenous and rectal routes. ... Meloxicam is metabolized to four biologically inactive metabolites and excreted in urine and feces ...

PMID:9105543

Turck D et al; Arzneimittelforschung 47 (3): 253-8 (1997).

This paper describes a study where the metabolism of the non-steroidal anti-inflammatory drug meloxicam was investigated in six horses and in the filamentous fungus Cunninghamella elegans. The metabolites identified were compared between the species, and then the fungus was used to produce larger amounts of the metabolites for future use as reference material. C. elegans proved to be a good model of phase I meloxicam metabolism in horses since all four metabolites found were the same in both species. Apart from the two main metabolites, 5'-hydroxymethylmeloxicam and 5'-carboxymeloxicam, a second isomer of hydroxymeloxicam and dihydroxylated meloxicam were detected for the first time in horse urine and the microbial incubations. Phase II metabolites were not discovered in the C. elegans samples but hydroxymeloxicam glucuronide was detected intact in horse urine for the first time in this study. Urine from six horses was further analyzed in a semi-quantitative sense and 5'-hydroxymethylmeloxicam gave peaks with much higher intensity compared to the parent drug and the other metabolites, and was detected for at least 14 days after the last given dose in some of the horses. ...

PMID:19291670

Tevell Aberg A et al; J Mass Spectrom 44 (7): 1026-37 (2009).

Appendix 7

4.2 Absorption, Distribution and Excretion (Complete)

The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg iv bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean Cmax was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (ie, Cmax) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (Tmax) was achieved between 5 and 6 hours.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

The mean volume of distribution (Vss) of meloxicam is approximately 10 L. Meloxicam is about 99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to about 99% in patients with renal disease.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of

this penetration is unknown.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam is distributed into milk in rats; discontinue nursing or drug because of potential risk in nursing infants.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Meloxicam crosses the placental barrier.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Plasma clearance ranges from 7 to 9 mL/min.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6% and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Elderly males (greater than or equal to 65 years of age) exhibited meloxicam plasma concentrations and steady state pharmacokinetics similar to young males. Elderly females (greater than or equal to 65 years of age) had a 47% higher AUCss and 32% higher Cmax /at steady-state/ as compared to younger females (greater than or equal to 55 years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam is not dialyzable.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

To assess the pharmacokinetic profile of single doses of meloxicam in healthy Chinese volunteers. The plasma concentrations of meloxicam after an oral dose of 15 mg to twenty healthy male volunteers were analyzed by means of a validated HPLC method. The pharmacokinetic parameters were subjected to Shapiro-Wilk test to determine whether these data were fitted to a normal distribution. The twenty volunteers can be classified into extensive metabolizers and poor metabolizers according to pharmacokinetic parameters. The main parameters in the two groups obtained were as follows: T 1/2 were 21 +/- 4 and 38 +/- 9 hr, AUC0-infinity were 49 +/- 10 and 110 +/- 8 ug.hr.mL-1, respectively. Even the AUC data in extensive metabolizers were 1.7 times as that reported in White volunteers following the same doses of meloxicam. There were significant individual differences in the pharmacokinetics of meloxicam in Chinese volunteers, which may be due to the genetic polymorphism of CYP2C9.

PMID:12579866

Xu HY et al; Yao Xue Xue Bao 36 (1): 71-3 (2001).

... The basic clinical pharmacokinetics of meloxicam (7.5-30 mg) have been investigated in 78 healthy male volunteers after single and multiple dosing via oral, intravenous and rectal routes. Plasma concentrations of meloxicam were determined by validated high performance liquid chromatography (HPLC) methods. The pharmaco-kinetic profile of meloxicam is characterized by almost complete absorption over a prolonged phase- avoiding high initial drug concentrations- and is bound to plasma proteins by more than 99.5%. ... This is reflected in a total plasma clearance of 7 to 8 mL/min. Steady state is achieved within 3 to 5 days. In addition, the pharmacokinetic parameters are linear over the entire dose range, there are no changes with multiple dosing and bioequivalence was shown for a number of different formulations. ...

PMID:9105543

Turck D et al; Arzneimittelforschung 47 (3): 253-8 (1997).

... Meloxicam is eliminated after biotransformation to 4 pharmacologically inactive metabolites, which are excreted in urine and feces. Meloxicam and its metabolites bind extensively to plasma albumin. Substantial concentrations of meloxicam are attained in synovial fluid, the proposed site of action in chronic inflammatory arthropathies. ...

PMID:10092958

Davies NM, Skjodt NM; Clin Pharmacokinet 36 (2): 115-26 (1999).

Appendix 7

4.3 Biological Half-Life (Complete)

The mean elimination half-life (t1/2) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

... The twenty volunteers can be classified into extensive metabolizers and poor metabolizers according to pharmacokinetic parameters. The main parameters in the two groups obtained were as follows: T 1/2 were 21 +/- 4 and 38 +/- 9 hr, respectively. ...

PMID:12579866

Xu HY et al; Yao Xue Xue Bao 36 (1): 71-3 (2001).

4.4 Mechanism of Action (Complete)

Meloxicam, an oxicam derivative that is structurally related to piroxicam, is a nonsteroidal anti-inflammatory agent (NSAIA) exhibiting analgesic, antipyretic, and anti-inflammatory actions. In vitro and in vivo studies indicate that meloxicam inhibits the cyclooxygenase-2 (COX-2) isoform of prostaglandin endoperoxide synthase (prostaglandin G/H synthase [PGHS]) to a greater extent than the COX-1 isoform. However, meloxicam's COX-2 selectivity is dose dependent and is diminished at higher dosages. Therefore meloxicam sometimes has been referred to as a "preferential" rather than "selective" COX-2 inhibitor.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

To investigate the effect of meloxicam on human polymorphonuclear leukocyte (PMN) adhesion to human synovial cell (HSC), and to explore its mechanism. MTT colorimetry was used to determine the adhesion effect of PMN to HSC. Cell-ELISA and RT-PCR methods were used to determine the expression of ICAM-1 and VCAM-1. Nuclear transcription factor-kappa B (NF-kappa B) was measured by electrophoretic mobility shift assay (EMSA) method. Meloxicam was found to effectively inhibit TNF-alpha (50 u.mL-1 for 12 hr) and IL-1 beta (50 u.mL-1 for 12 hr)-induced adhesion of PMN to HSC (IC50 3.38 X 10(-7) mol.L-1 and 3.56 X 10(-6) mol.L-1, respectively) in a concentration-dependent manner. ICAM-1 protein and mRNA expression induced by TNF-alpha (50 u.mL-1) were inhibited by meloxicam at 1 X 10(-6)-1 X 10(-5) mol.L-1. The activation of NF-kappa B was also inhibited by meloxicam at 1 X 10(-6)-1 X 10(-5) mol.L-1. These results suggest that meloxicam inhibit TNF-alpha stimulated PMN-HSC adhesion and expression of ICAM-1 by suppressing the activity of NF-kappa B.

Appendix 7

PMID:12579952

Li LC et al; Yao Xue Xue Bao 37 (2): 103-7 (2002).

/Investigators/ compared the effects of therapeutically equivalent doses of meloxicam and indomethacin, a preferential inhibitor of the constitutive cyclooxygenase (COX-1), on platelet aggregation and platelet thromboxane formation, which are exclusively COX-1 dependent, physiological renal, and total body prostaglandin E2 (PGE2) production. In a randomized cross-over design, 14 healthy female volunteers received meloxicam 7.5 mg per day for 6 days or indomethacin 25 mg three times per day for 3 days; the wash-out period was 5 days, and drug intake was adapted to the menstrual cycle. On the day before treatment and on the last day of each treatment period the following parameters were evaluated: maximum platelet aggregation and thromboxane B2 (TXB2) formation in response to 1.0 mmol/L arachidonic acid; 24-hour urinary excretion of PGE2 and 7 alpha-hydroxy-5, 11-diketo-tetranor-prosta-1, 16-dionic acid (PGE-M), the index metabolites of renal and total body PGE2 synthesis, respectively, were assessed by gas chromatography/tandem mass spectrometry. Maximum platelet aggregation and TXB2 formation were almost completely inhibited by indomethacin (-87% and -99%, respectively; $p < 0.001$, each) as compared to control (100%), but remained unaffected by meloxicam (-1% and +4%, respectively). Meloxicam showed no significant effects on urinary PGE2 excretion (-13%) and only slight effects on PGE-M excretion (-22%; $p < 0.05$), whereas indomethacin reduced urinary PGE2 excretion (-43%; $p < 0.05$) as well as PGE-M excretion (-36%; $p < 0.001$). /This/ data shows, that meloxicam 7.5 mg per day is COX-1 sparing in humans in vivo.

PMID:9084574

Stichtenoth DO et al; J Investig Med 45 (2): 44-9 (1997).

5 Pharmacology

5.1 Therapeutic Uses (Complete)

Thiazines, Thiazoles; Isoenzymes/antagonists & inhibitors

National Library of Medicine's Medical Subject Headings online file (MeSH, 2009)

Meloxicam is indicated for relief of the signs and symptoms of osteoarthritis. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. /Included in US product label/

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam is used for the management of the signs and symptoms of rheumatoid arthritis

in adults. In the management of rheumatoid arthritis in adults, NSAIAs may be useful for initial symptomatic treatment; however, NSAIAs do not alter the course of the disease or prevent joint destruction. /Included in US product label/

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2161

Meloxicam is used for the management of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis in children 2 years of age or older. /NOT included in US product label/

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2161

Meloxicam also has been used in the management of ankylosing spondylitis. /Not included in US product label/

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2161

/VET/ Osteoarthritis is a chronic, painful condition that is now recognised as affecting a large proportion of cats. Non-steroidal anti-inflammatory drugs (NSAIDs) have proven efficacy in dogs and humans but there are limited published data on the use of NSAIDs in the long-term management of this condition in cats. This prospective study aimed to assess the long-term safety and palatability of oral meloxicam and its efficacy in treating osteoarthritic pain in cats when given at a dose of 0.01-0.03 mg/kg once daily. Forty cats diagnosed with osteoarthritis completed the trial with a mean treatment duration of 5.8 months. Gastrointestinal upset in 2/46 (4%) cats was the only adverse effect noted. No deleterious effect on renal function was detected in cats studied. Owners subjectively assessed treatment efficacy as good or excellent in 34/40 (85%) of cases. The results of this study showed oral meloxicam to be safe and palatable long-term treatment for osteoarthritis in cats when given with food at a dose of 0.01-0.03 mg/kg.

PMID:18440263

Gunew MN et al; J Feline Med Surg 10 (3): 235-41 (2008).

/VET/ The antipyretic efficacy of meloxicam was evaluated in a feline endotoxin model using a replicated change-over design. Twelve adult cats of both sexes were allocated at random to three experimental groups. At 30 min prior to the intravenous (i.v.) endotoxin challenge (0.5 microgram/kg body weight(b.w.)), 2 animals in each group received an i.v. injection of 0.1, 0.3 or 0.5 mg meloxicam/kg b.w. and the two remaining animals in each group received physiological saline. In a second phase, 21 days later, the meloxicam/placebo treatment was exchanged within each group. The rectal temperature and scores for general demeanour were determined at 30-min intervals from before dosing to 300 min after the endotoxin challenge. Hematological parameters were analysed before and 60 min after administration of endotoxin. The results indicated a significant dose-dependent antipyretic response to

meloxicam after endotoxin challenge. The antipyretic response in the medium- and high-dose meloxicam groups did not differ significantly, but both were significantly different from the low-dosage group. The individual effects of endotoxin on general demeanour were rather variable but meloxicam tended to have a beneficial effect. Endotoxin induced a reduction in the white blood cell count but this was not influenced by meloxicam. It was concluded that the pyretic endotoxin model is very suitable for studying new NSAIDs in cats and that the optimum single dose of meloxicam in this model was 0.3 mg/kg b.w.

PMID:8540243

Justus C, Quirke JE; Vet Res Commun 19 (4): 321-30 (1995).

5.2 Drug Warnings (Complete)

/BOXED WARNING/ WARNING: Cardiovascular Risk NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Meloxicam is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (Updated: May 2010). Available from, as of April 24, 2015: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6513e46b-3229-685b-c83b-2209454fae71

/BOXED WARNING/ WARNING: Gastrointestinal Risk: NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (Updated: May 2010). Available from, as of April 24, 2015: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6513e46b-3229-685b-c83b-2209454fae71

Contraindications: Known hypersensitivity to meloxicam or any ingredient in the formulation. History of urticaria, angioedema, bronchospasm, severe rhinitis, or shock precipitated by aspirin or other NSAIAs. History of aspirin triad (aspirin sensitivity, asthma, and nasal polyps). Treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Selective COX-2 inhibitors have been associated with an increased risk of serious adverse cardiovascular thrombotic events in certain situations. Several prototypical NSAIAs also

have been associated with an increased risk of cardiovascular events. Findings from a recent systematic review of controlled observational studies and a meta-analysis of published and unpublished data from randomized studies of these agents suggest that use of celecoxib (dosage exceeding 200 mg daily), diclofenac, or indomethacin is associated with an increased risk of cardiovascular events. The possibility exists that meloxicam and ibuprofen also are associated with increased cardiovascular risk.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at increased risk for NSAIA-associated cardiovascular events. To minimize the potential risk of adverse cardiovascular events, use the lowest effective dosage and shortest possible duration of therapy. Clinicians and patients receiving NSAIAs (including those without previous symptoms of cardiovascular disease) should remain alert to the possible development of cardiovascular events. Short-term use of NSAIAs to relieve acute pain, especially at low dosages, does not appear to be associated with an increased risk of serious cardiovascular events (except immediately following CABG surgery). There is no consistent evidence that concomitant use of low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIAs.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Use of NSAIAs, including meloxicam, can result in the onset of hypertension or worsening of preexisting hypertension; either of these occurrences may contribute to the increased incidence of cardiovascular events. Patients receiving NSAIAs and diuretics (ie, thiazide or loop diuretics) may have an impaired response to the diuretic. Use NSAIAs, including meloxicam, with caution in patients with hypertension. Monitor blood pressure closely during initiation of meloxicam therapy and throughout therapy.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Use with caution in patients with fluid retention or heart failure, since fluid retention and edema have been observed in some patients receiving the drug.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Risk of serious GI effects (eg, bleeding, ulceration, perforation), which can occur at any time with or without warning signs or symptoms. Conditions or concomitant therapies that may increase risk include a history of GI bleeding or ulceration, longer duration of NSAIA therapy, treatment with anticoagulants or oral corticosteroids, smoking, alcohol dependence, poor general health, or older age (higher risk of fatal GI complications). Use with extreme caution in these patients. In some clinical studies, meloxicam was associated

with a lower incidence of adverse GI effects compared with other NSAIAs (eg, diclofenac, naproxen, piroxicam).

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Renal papillary necrosis or other renal medullary changes may occur with long-term administration of NSAIAs. Possibility of overt renal decompensation in patients dependent on renal prostaglandins for maintenance of renal perfusion. Patients at particular risk include those with heart failure, hepatic or renal dysfunction, or dehydration; those receiving a diuretic, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin II antagonist; and geriatric patients. Recovery of renal function to pretreatment levels usually occurs following discontinuance of NSAIA therapy.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Sensitivity reactions, including anaphylactoid reactions, possible in patients without prior exposure to meloxicam. Immediate medical intervention and drug discontinuance required. Cross-sensitivity may exist with other NSAIAs. ... Serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) can occur in patients receiving meloxicam. These serious skin reactions may occur without warning. Discontinue meloxicam at the first appearance of rash or any other sign of hypersensitivity.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Borderline elevations of one or more liver function tests may occur in up to 15% of patients treated with NSAIAs, including meloxicam; meaningful (3 times the upper limit of normal) elevations of serum ALT (SGT) or AST (SGOT) reported in approximately 1% of patients receiving other NSAIAs. Severe, sometimes fatal, reactions (eg, jaundice, fulminant hepatitis, liver necrosis, hepatic failure) reported rarely in patients receiving NSAIAs. Discontinue use if clinical signs and symptoms occur.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Anemia has been reported, principally in patients receiving long-term (eg, 6 months' duration) therapy with meloxicam. Notable effects on platelets or bleeding times do not appear to occur.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

May mask certain signs of infection; cannot be used as a substitute for corticosteroid therapy nor used to treat adrenal insufficiency.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Meloxicam is distributed into milk in rats; discontinue nursing or drug because of potential risk in nursing infants.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

If meloxicam must be used in patients with advanced renal disease, closely monitor renal function.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

Adverse effects occurring in 2% or more of adults receiving meloxicam include dyspepsia, headache, nausea, diarrhea, upper respiratory tract infection, abdominal pain, dizziness, edema, flatulence, influenza-like illness, musculoskeletal and connective tissue signs and symptoms (back pain, muscle spasms, musculoskeletal pain), and rash.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

The most common adverse effects reported in pediatric patients include abdominal pain, vomiting, diarrhea, headache, and pyrexia.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

FDA Pregnancy Risk Category: C /RISK CANNOT BE RULED OUT. Adequate, well controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is given during pregnancy; but the potential benefits may outweigh the potential risk./

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Meloxicam should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Caution should be used when initiating treatment with meloxicam in patients with

considerable dehydration. It is advisable to rehydrate patients first and then start therapy with meloxicam. Caution is also recommended in patients with pre-existing kidney disease.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving meloxicam who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, meloxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, meloxicam should be discontinued.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate. In vitro, methotrexate did not displace meloxicam from its human serum binding sites.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

5.3 Interactions (Complete)

When meloxicam is administered with aspirin to healthy volunteers, it tended to increase the AUC (10%) and Cmax (24%) of meloxicam. The clinical significance of this interaction is not known; however, as with other NSAIDs concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Concomitant administration of low-dose aspirin with meloxicam may result in an increased rate of GI ulceration or other complications, compared to use of meloxicam alone. Meloxicam is not a substitute for aspirin for cardiovascular prophylaxis.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t1/2, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium ... BID with meloxicam ... QD as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by meloxicam. Patients on lithium treatment should be closely monitored for signs of lithium toxicity when meloxicam is introduced, adjusted, or withdrawn.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

Twelve healthy volunteers in a crossover study ingested 15 mg of meloxicam without pretreatment (control), after voriconazole pretreatment, and after itraconazole pretreatment. The plasma concentrations of meloxicam, voriconazole, itraconazole, and

thromboxane B(2) (TxB(2)) generation were monitored. Compared to the control phase, voriconazole increased the mean area under the plasma concentration-time curve from 0 to 72 hr (AUC(0-72)) of meloxicam by 47% (P < 0.001) and prolonged its mean half-life (t(1/2)) by 51% (P < 0.01), without affecting its mean peak concentration (C(max)). In contrast, itraconazole decreased the mean AUC(0-72) and C(max) of meloxicam by 37% (P < 0.001) and by 64% (P < 0.001), respectively, and prolonged its t(1/2) and time to C(max). The plasma protein unbound fraction of meloxicam was unchanged by voriconazole and itraconazole. Lowered plasma meloxicam concentrations during the itraconazole phase were associated with decreased pharmacodymic effects of meloxicam, as observed by weaker inhibition of TxB(2) synthesis compared to the control and voriconazole phases. Voriconazole increases plasma concentrations of meloxicam, whereas itraconazole, unexpectedly, decreases plasma meloxicam concentrations, possibly by impairing its absorption.

PMID:19015346

Full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2630625

Hynninen VV et al; Antimicrob Agents Chemother 53 (2): 587-92 (2009).

The influence of multiple oral doses of cholestyramine on the single dose pharmacokinetics of meloxicam has been studied in 12 healthy male volunteers. Each subject received on two occasions a single iv injection of meloxicam 30 mg. The cholestyramine group received the material suspended in water 3 times a day. Compared to controls, cholestyramine accelerated the elimination of meloxicam. The mean terminal phase elimination half-life was reduced from 19.5 hr to 12.7 hr due to an increase in clearance of the drug (0.426 vs 0.636 L.hr-1). Also, as a consequence of increased clearance in the presence of cholestyramine, the mean residence time of the drug in the body was significantly decreased (39%) P < 0.01. However, the volume of distribution for meloxicam was largely unaffected by cholestyramine which suggests that meloxicam undergoes gut recirculation. ...

PMID:7589053

Busch U et al;

6 Environmental Fate & Exposure

6.1 Environmental Fate / Exposure Summary

Meloxicam's production and use as an antiinflammatory may result in its release to the environment through various waste streams. If released to air, an estimated vapor pressure of 1.1X10-15 mm Hg at 25 °C indicates meloxicam will exist solely in the particulate phase in the atmosphere. Particulate-phase meloxicam will be removed from the atmosphere by wet or dry deposition. Meloxicam does not contain chromophores that absorb at

wavelengths >290 nm and theefore is not expected to be susceptible to direct photolysis by sunlight. If released to soil, meloxicam is expected to have slight mobility based upon an estimated Koc of 1,700. Estimated values of pKa1 of 3.8 and pKa2 of 7.6 suggest that meloxicam will exist as a zwitterion in the environment. Volatilization from moist soil is not expected because the base exists as an ion and ions do not volatilize. Meloxicam may not volatilize from dry soil surfaces based upon its vapor pressure. Biodegadation data were not available. If released into water, meloxicam is expected to adsorb to suspended solids and sediment based upon the estimated Koc. The estimated pKa values indicate meloxicam will exist in the zwitterion form at pH values of 5 to 9 and therefore volatilization from water surfaces is not expected to be an important fate process. An estimated BCF of 85 suggests the potential for bioconcentration in aquatic organisms is moderate. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions. Occupational exposure to meloxicam may occur through inhalation and dermal contact with this compound at workplaces where meloxicam is produced or used. Exposure to meloxicam among the general population may be limited to those administered the drug Mobic, a non-steroidal antiinflammatory. (SRC)

6.2 Probable Routes of Human Exposure (Complete)

Occupational exposure to meloxicam may occur through inhalation and dermal contact with this compound at workplaces where meloxicam is produced or used. Exposure to meloxicam among the general population may be limited to those administered the drug Mobic, a non-steroidal antiinflammatory. (SRC)

6.3 Artificial Pollution Sources (Complete)

Meloxicam's production and use as an anitinflammatory(1) may result in its release to the environment through various waste streams(SRC).

(1) O'Neil MJ, ed; The Merck Index. 14th ed., Whitehouse Station, NJ: Merck and Co., Inc., p. 1006 (2006)

6.4 Environmental Fate (Complete)

TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 1,700(SRC), determined from a log Kow of 3.43(2) and a regression-derived equation(3), indicates that meloxicam is expected to have slight mobility in soil(SRC). Estimated values of pKa1 of 3.8 and pKa2 of 7.6(4) suggest that meloxicam will exist as a zwitterion in the environment.. Volatilization from moist soil is not expected because the acid exists as an ion and ions do not volatilize. Meloxicam is not expected to volatilize from dry soil

surfaces(SRC) based upon an estimated vapor pressure of 1.1X10-15 mm Hg at 25 °C(SRC), determined from a fragment constant method(5). Biodegradation data were not available(SRC, 2009).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Avdeef A; Seminar on Ionixation and Lipophilicity. Log P values measured by pION Inc., Brookline, MA (A. Avdeef and C. Berger) (1997) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9 (1990) (4) SPARC; pKa/property server. Ver 4.2 Mar, 2008. Available from, as of Nov 16, 2009: https://ibmlc2.chem.uga.edu/sparc/ (5) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 1,700(SRC), determined from a log Kow of 3.43(2) and a regression-derived equation(3), indicates that meloxicam is expected to adsorb to suspended solids and sediment(SRC). The estimated pKa values of pKa1 of 3.8 and pKa2 of 7.6(4) indicate meloxicam will exist in the zwitterion form at pH values of 5 to 9 and therefore volatilization from water surfaces is not expected to be an important fate process. According to a classification scheme(5), an estimated BCF of 85(SRC), from its log Kow(2) and a regression-derived equation(6), suggests the potential for bioconcentration in aquatic organisms is moderate(SRC). Biodegradation data were not available(SRC, 2008).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Avdeef A; Seminar on Ionixation and Lipophilicity. Log P values measured by pION Inc., Brookline, MA (A. Avdeef and C. Berger) (1997) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9, 15-1 to 15-29 (1990) (4) SPARC; pKa/property server. Ver 4.2 Mar, 2008. Available from, as of Nov 16, 2009: https://ibmlc2.chem.uga.edu/sparc/ (5) Franke C et al; Chemosphere 29: 1501-14 (1994) (6) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999)

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), meloxicam, which has an estimated vapor pressure of 1.1X10-15 mm Hg at 25 °C(SRC), determined from a fragment constant method(2), is expected to exist solely in the particulate phase in the ambient atmosphere. Particulate-phase meloxicam may be removed from the air by wet or dry deposition(SRC). Meloxicam does not contain chromophores that absorb at wavelengths >290 nm(4) and therefore is not expected to be susceptible to direct photolysis by sunlight(SRC).

(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985) (3) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993) (4) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 8-12 (1990)

6.5 Environmental Abiotic Degradation (Complete)

Meloxicam is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions(3). Meloxicam does not

contain chromophores that absorb at wavelengths >290 nm(3) and therefore is not expected to be susceptible to direct photolysis by sunlight(SRC).

(1) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 7-4, 7-5, 8-12 (1990)

6.6 Environmental Bioconcentration (Complete)

An estimated BCF of 85 was calculated in fish for meloxicam(SRC), using log Kow of 3.43(1) and a regression-derived equation(2). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is moderate(SRC).

(1) Avdeef A; Seminar on Ionixation and Lipophilicity. Log P values measured by pION Inc., Brookline, MA (A. Avdeef and C. Berger) (1997) (2) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999) (3) Franke C et al; Chemosphere 29: 1501-14 (1994)

6.7 Soil Adsorption / Mobility (Complete)

The Koc of meloxicam is estimated as 1,700(SRC), using a log Kow of 3.43(1) and a regression-derived equation(2). According to a classification scheme(3), this estimated Koc value suggests that meloxicam is expected to have slight mobility in soil.Estimated values of pKa1 of 3.8 and pKa2 of 7.6(4) suggest that meloxicam will exist as a zwitterion in the environment.

(1) Meylan WM et al; Environ Sci Technol 26: 1560-67 (1992) (2) Avdeef A; Seminar on Ionixation and Lipophilicity. Log P values measured by pION Inc., Brookline, MA (A. Avdeef and C. Berger) (1997) (3) Swann RL et al; Res Rev 85: 17-28 (1983) (4) SPARC; pKa/property server. Ver 4.2 Mar, 2008. Available from, as of Nov 16, 2009: https://ibmlc2.chem.uga.edu/sparc/

6.8 Volatilization from Water / Soil (Complete)

The estimated pKa values of pKa1 of 3.8 and pKa2 of 7.6(1) indicate meloxicam will exist in the zwitterion form at pH values of 5 to 9 and therefore volatilization from water surfaces is not expected to be an important fate process. Meloxicam is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 1.1X10-15 mm Hg(SRC), determined from a fragment constant method(2).

(1) SPARC; pKa/property server. Ver 4.2 Mar, 2008. Available from, as of Nov 16, 2009: https://ibmlc2.chem.uga.edu/sparc/ (2) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

6.9 Environmental Water Concentrations (Complete)

While data specific to meloxicam were not located(SRC, 2009), the literature suggests that some pharmaceutically active compounds originating from human and veterinary therapy are not eliminated completely in municipal sewage treatment plants and are therefore discharged into receiving waters(1). Wastewater treatment processes often were not designed to remove them from the effluent(2). Selected organic waste compounds may be degrading to new and more persistent compounds that may be released instead of or in addition to the parent compound(2).

(1) Heberer T; Tox Lett 131: 5-17 (2002) (2) Koplin DW et al; Environ Sci Toxicol 36: 1202-211 (2002)

6.10 Milk Concentrations (Complete)

Meloxicam is distributed into milk in rats; discontinue nursing or drug because of potential risk in nursing infants.

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2162

7 Environmental Standards & Regulations

7.1 FDA Requirements (Complete)

Meloxicam ... Indications for use /in dogs/: For the control of pain and inflammation associated with osteoarthritis. ... Limitations: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

21 CFR 520.1350 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 24, 2009: https://www.ecfr.gov

Meloxicam. ... Indications for use /in dogs/: For the control of pain and inflammation associated with osteoarthritis. ... Federal law restricts this drug to use by or on the order of a licensed veterinarian. ... Indications for use /in cats/: For the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration when administered prior to surgery. ... Limitations: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

21 CFR 522.1367 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 24, 2009: https://www.ecfr.gov

The Approved Drug Products with Therapeutic Equivalence Evaluations List identifies currently marketed prescription drug products, incl meloxicam, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act.

Appendix 7

DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of July 9, 2009: https://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm

The Generic Animal Drug and Patent Restoration act requires that each sponsor of an approved animal drug must submit to the FDA certain information regarding patents held for the animal drug or its method of use. The Act requires that this information, as well as a list of all animal drug products approved for safety and effectiveness, be made available to the public. Meloxicam is included on this list.

US FDA/Center for Veterinary Medicine; The Green Book - On Line, Active Ingredients. Meloxicam (71125-38-7). Available from, as of July 9, 2009: https://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/default.htm

8 Chemical / Physical Properties

8.1 Molecular Formula

C_{14}-H_{13}-N_3-O_4-S_2

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006.

8.2 Molecular Weight

351.40

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

8.3 Color / Form (Complete)

Crystals from ethylene chloride

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

Pastel yellow solid

Wishart DS et al; DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 1;34. Available from, as of Apr 23, 2009: https://www.drugbank.ca

8.4 Melting Point

254 °C (decomposes)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse

Appendix 7

Station, NJ: Merck and Co., Inc., 2006., p. 1006

8.5 LogP

log Kow = 3.54

Avdeef A; Seminar on Ionixation and Lipophilicity. Log P values measured by pION Inc., Brookline, MA (A. Avdeef and C. Berger) (1997)

8.6 Dissociation Constants

pKa = 4.08 in water; 4.24 in water/ethanol (1:1); 4.63 in water/ethanol (1:4)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

8.7 Solubility (Complete)

Very slightly soluble in methanol. Practically insoluble in water, with higher solubility observed in strong acids and bases.

Wishart DS et al; DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 1;34. Available from, as of Apr 23, 2009: https://www.drugbank.ca

9 Chemical Safety & Handling

9.1 Storage Conditions (Complete)

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

9.2 Disposal Methods (Complete)

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.

10 Manufacturing / Use Information

Appendix 7

10.1 Uses (Complete)

Nonsteroidal anti-inflammatory drug used to relieve the symptoms of arthritis, primary dysmenorrhea, fever, and as an analgesic ...

Wishart DS et al; DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 1;34. Available from, as of Apr 22, 2009: https://www.drugbank.ca

THERAP CAT: Anti-inflammatory

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

THERAP CAT (VET): Anti-inflammatory

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

Medication

10.2 Manufacturers

Boehringer Ingelheim, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368, (800) 243-0127 /Formulator/

Thomson Health Care Inc.; Physicians' Desk Reference 63 ed., Montvale, NJ 2009, p. 863

Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Rd., Morgantown, WV 26504-4310, (877) 446-3679 /Formulator/

Thomson Health Care Inc.; Physicians' Desk Reference 63 ed., Montvale, NJ 2009, p. 2177

10.3 Methods of Manufacturing (Complete)

Reaction of benzothiazolo-3(2H)-one-1,1-dioxide with methyl chloroacetate gives the methyl 2(3H)-acetate derivative, which is isomerized with sodium methoxide in toluene-tert-butanol yielding methyl 4-hydroxy-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide. Subsequent methylation with methyl iodide in methanol yields the 2-methyl compound. Finally this compound is treated with 2-amino-5-methylthiazole in xylene.

Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V3 51 (2003)

Preparation: G. Trummlitz et al., DE 2756113 (1979 to Thomae); eidem, US 4233299 (1980 to Boehringer Ingelheim).

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

Appendix 7

10.4 Formulations / Preparations (Complete)

Formulations: (AHFS, 2009)

Route of administration	Dosage Form	Strength	Brand (Manufacturer)
Oral	Tablets	7.5 mg	Mobic (Boehringer Ingelheim)
Oral	Tablets	15 mg	Mobic (Boehringer Ingelheim)
Oral	Suspension	7.5/5 mL	Mobic (Boehringer Ingelheim)

American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009), p. 2163

11 Laboratory Methods

11.1 Clinical Laboratory Methods (Complete)

Analyte: meloxicam; matrix: blood (plasma); procedure: high-performance liquid chromatography with ultraviolet detection at 355 nm; limit of quanitation: 50 ng/mL

Busch U et al; Drug Metab Dispos 26: 576-584 (1998). As cited in: Lunn G; HPLC and CE Methods for Pharmaceutical Analysis. CD-ROM. New York, NY: John Wiley & Sons (2000)

11.2 Analytic Laboratory Methods (Complete)

Analyte: meloxicam; matrix: chemical identification; procedure: infrared absorption spectrophotometry with comparison to standards

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2607 (2008)

Analyte: meloxicam; matrix: chemical identification; procedure: ultraviolet absorption spectrophotometry at 240 to 450 nm with comparison to standards

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2607 (2008)

Analyte: meloxicam; matrix: chemical purity; procedure: liquid chromatography with UV detection at 360 nm with comparison to standards

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2607 (2008)

Analyte: meloxicam; matrix: pharmaceutical preparation (oral suspension, tablet); procedure: thin-layer chromatography with UV detection at 254 nm and comparison to standards

(chemical identification)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2609 (2008)

Analyte: meloxicam; matrix: pharmaceutical preparation (oral suspension, tablet); procedure: retention time of the major peak of the liquid chromatogram with comparison to standards (chemical identification)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2609 (2008)

Analyte: meloxicam; matrix: pharmaceutical preparation (oral suspension); procedure: liquid chromatography with UV detection at 260 nm and 360 nm with comparison to standards (chemical purity)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2609 (2008)

Analyte: meloxicam; matrix: pharmaceutical preparation (tablet); procedure: liquid chromatography with ultraviolet detection at 254 nm and comparison to standards (chemical purity)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 31/The National Formulary, NF 26; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p.2609 (2008)

12 Synonyms and Identifiers

Synonyms

71125-38-7

Meloxicam

4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benothiazine-3-carboxamide 1,1-dioxide

Metacam

Mobec

Mobic

12.1 Substance Title

Meloxicam

13 Administrative Information

Appendix 7

13.1 Hazardous Substances DataBank Number

7741

13.2 Last Revision Date

20091218

13.3 Last Review Date

Reviewed by SRP on 9/10/2009

13.4 Update History

Field Update on 2016-04-11, 1 fields added/edited/deleted

Complete Update on 2009-12-18, 40 fields added/edited/deleted

Created 20090413

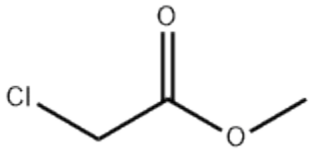
Appendix 7

CONTENTS

Title and Summary
1 Human Health Effects
2 Emergency Medical Treatment
3 Animal Toxicity Studies
4 Metabolism/ Pharmacokinetics
5 Pharmacology
6 Environmental Fate & Exposure
7 Environmental Standards & Regulations
8 Chemical/Physical Properties
9 Chemical Safety & Handling
10 Manufacturing/Use Information
11 Laboratory Methods
12 Synonyms and Identifiers
13 Administrative Information

ChemicalBook >> CAS DataBase List >>Methyl chloroacetate

Methyl chloroacetate



Methyl chloroacetate structure

CAS No.
96-34-4

Chemical Name:
Methyl chloroacetate

Synonyms
methyl 2-chloroacetate;MONO METHYL CHLORO ACETATE;METHYL MONOCHLOROACETATE;IHT-FC MCA;Chloroacetic acid methyl;CHLOROACETIC ACID METHYL ESTER;ClH2CCOOCH3;AKOS BBS-00004061;Methylechloroacetate;Mathyl Chloroacetate

CBNumber:
CB9854725

Molecular Formula:
C3H5ClO2

Molecular Weight:
108.52

MDL Number:
MFCD00000931

MOL File:
96-34-4.mol

Last updated:2023-11-28 16:31:44

Methyl chloroacetate Chemical Properties,Uses,Production

Chemical Properties

clear colorless liquid with a slight irritating odor. It is miscible with organic solvents such as ethanol, ether, acetone and benzene. Slightly soluble in water.

Uses

Methyl chloroacetate is used as a solvent and chemical intermediate. It acts as a precursor in the preparation of (carboxymethyl) trimethylammonium chloride esters. Further, it is used in the preparation of octakis-(carbethoxymethoxy)calix[8]arene. It is employed as an extraction solvent during the separation of neutral compounds. In addition to this, it is used in the synthesis of dimethyl carbonate.

Application

Methyl chloroacetate (MC) is a halogenated ester mainly used as a solvent in organic synthesis or in the preparation of several compounds. Typically, MC is used in the preparation of (carboxymethyl) trimethylammonium chloride estersor in the synthesis of octakis-(carbethoxymethoxy)calix[8]arene. Additionally, methyl chloroacetate acts as an extraction solvent during the separation of neutral compounds with concentration enhancement using coupling liquid–liquid semi-microextraction with micellar electrokinetic chromatography through oncapillary decomposition.

Preparation

Methyl chloroacetate is prepared by esterification of chloroacetic acid with methanol. Reaction: Methanol and chloroacetic acid are uniformly mixed in a weight ratio of 0.366:1, heated with stirring, and the esterification reaction is carried out at 105-110 °C. In the reaction process, the ternary azeotrope of methyl chloroacetate, water and methanol is continuously steamed, layered through the ester separator, the separated methanol and water are returned to the reaction pot, and the separated crude ester is made of sodium carbonate. neutralize. The neutralized crude ester is firstly cut out the 130°C fraction by atmospheric distillation, and then subjected to vacuum distillation to collect the 65°C (8kPa) fraction, which is the finished product of methyl chloroacetate. The yield is about 96%.

Synthesis Reference(s)

The Journal of Organic Chemistry, 50, p. 3408, 1985 **DOI:** 10.1021/jo00218a034

General Description

A crystalline solid or a solid dissolved in a liquid. Insoluble in water and denser than water. Contact may slightly irritate skin, eyes and mucous membranes. May be slightly toxic by ingestion. Used to make other chemicals.

Air & Water Reactions

Highly flammable. Insoluble in water.

Reactivity Profile

Methyl chloroacetate is a halogenated ester. Esters react with acids to liberate heat along with alcohols and acids. Strong oxidizing acids may cause a vigorous reaction that is sufficiently exothermic to ignite the reaction products. Heat is also generated by the interaction of esters with caustic solutions. Flammable hydrogen is generated by mixing esters with alkali metals and hydrides.

Hazard

Toxic by ingestion and inhalation.

Health Hazard

Extremely corrosive to the eyes, skin, nose, throat, and upper respiratory tract. Inhalation may be fatal as a result of spasm, inflammation and edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema. Symptoms of exposure include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting.

Fire Hazard

Special Hazards of Combustion Products: Toxic fumes of hydrogen chloride

Safety Profile

Poison by ingestion. Moderately toxic by inhalation and subcutaneous routes. Flammable when exposed to heat or flame; can react vigorously with oxidizing materials. When heated to decomposition it emits toxic fumes of Cl-.

Purification Methods

Shake the ester with saturated aqueous Na2CO3 (three times), aqueous 50% CaCl2 (three times), saturated aqueous NaCl (twice), dry (Na2SO4) and fractionally distil it. Very toxic. [Beilstein 2 IV 480.]

Appendix 9

Displaying title 21, up to date as of 1/23/2024. Title 21 was last amended 1/22/2024.

Title 21 —Food and Drugs
Chapter I —Food and Drug Administration, Department of Health and Human Services
Subchapter A —General
Part 25 —Environmental Impact Considerations
Subpart C —Categorical Exclusions

EDITORIAL NOTE ON PART 25

Editorial Note: Nomenclature changes to part 25 appear at 88 FR 45065, July 14, 2023.

§ 25.33 Animal drugs.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NADA, abbreviated application, request for determination of eligibility for indexing, a supplement to such applications, or a modification of an index listing, if the action does not increase the use of the drug. Actions to which this categorical exclusion applies may include:

(1) An animal drug to be marketed under the same conditions of approval as a previously approved animal drug;

(2) A combination of previously approved animal drugs;

(3) A new premix or other formulation of a previously approved animal drug;

(4) Changes specified in § 514.8(b)(3), (b)(4), or (c)(3) of this chapter;

(5) A change of sponsor; or

(6) A previously approved animal drug to be contained in medicated feed blocks under § 510.455 of this chapter or as a liquid feed supplement under § 558.5 of this chapter.

(b) [Reserved]

(c) Action on an NADA, abbreviated application, request for determination of eligibility for indexing, a supplement to such applications, or a modification of an index listing, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Action on an NADA, abbreviated application, request for determination of eligibility for indexing, a supplement to such applications, or a modification of an index listing, for:

(1) Drugs intended for use in nonfood animals;

(2) Anesthetics, both local and general, that are individually administered;

Appendix 9

(3) Nonsystemic topical and ophthalmic animal drugs;

(4) Drugs for minor species, including wildlife and endangered species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used; and

(5) Drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species.

(e) Action on an INAD.

(f) Action on an application submitted under section 512(m) of the act.

(g) Withdrawal of approval of an NADA or an abbreviated NADA or removal of a new animal drug from the index.

(h) Withdrawal of approval of a food additive petition that reduces or eliminates animal feed uses of a food additive.

[62 FR 40592, July 29, 1997, as amended at 71 FR 74782, Dec. 13, 2006; 72 FR 69119, Dec. 6, 2007; 85 FR 72907, Nov. 16, 2020]

the Commission to ''consider the costs and benefits'' of its action.

Section 15(a) further specifies that costs and benefits shall be evaluated in light of five broad areas of market and public concern: Protection of market participants and the public; efficiency, competitiveness, and financial integrity of futures markets; price discovery; sound risk management practices; and other public interest considerations. Accordingly, the Commission could in its discretion give greater weight to any one of the five enumerated areas and could in its discretion determine that, notwithstanding its costs, a particular rule was necessary or appropriate to protect the public interest or to effectuate any of the provisions or to accomplish any of the purposes of the Act.

The Commission is considering the costs and benefits of these rules in light of the specific provisions of Section 15(a) of the Act:

1. Protection of Parket Participants and the Public

The amendments being adopted herein are not expected to result in less protection of market participants or the public. Rather, the amendments provide the opportunity for a more meaningful and accurate disclosure, as demanded by marketplace forces. Moreover, the Commission, along with NFA, will continue to monitor the presentation of performance by CTAs and take action wherever necessary.

2. Efficiency and Competition

The amendments are expected to increase efficiency by providing a CTA with increased flexibility for providing past performance. With this flexibility, a CTA will be better able to respond to changes in the industry and demands from the marketplace with regard to the disclosure of the CTA's past performance.

3. Financial Integrity of Futures Markets and Price Discovery

The amendments should have no effect, from the standpoint of imposing costs or creating benefits, on the financial integrity or price discovery function of the commodity futures and options markets.

4. Sound Risk Management Practices

The amendments should have no effect on sound risk management practices.

5. Other Public Interest Considerations

The amendments being adopted herein provide more flexibility for CTAs in being able to present past performance in a manner that more accurately represents the trading results of their systems, while maintaining adequate safeguards so as to protect prospective clients from misleading or fraudulent solicitations.

After considering these factors, the Commission has determined to issue the amended rules.

List of Subjects in 17 CFR Part 4

Advertising, Commodity Futures, Customer Protection, Reporting and recordkeeping.

■ For the reasons discussed in the foregoing, the Commission hereby amends Chapter I of Title 17 of the Code of Federal Regulations as follows:

PART 4—COMMODITY POOL OPERATORS AND COMMODITY TRADING ADVISORS

■ 1. The authority citation for Part 4 continues to read as follows:

Authority: 7 U.S.C. 1a, 2, 6(c), 6b, 6c, 6l, 6m, 6n, 6o, 12a and 23.

■ 2. Section 4.10 is amended by adding paragraph (m) to read as follows:

§ 4.10 Definitions.

* * * * *

(m) *Partially-funded account* means a client participation in the program of a commodity trading advisor in which the amount of funds in the client's commodity interest account over which such commodity trading advisor has trading authority is less than the account size that establishes the client's level of trading in a commodity trading advisor's program.

■ 3. Section 4.25 is amended by adding paragraph (a)(1)(ii)(H) to read as follows:

§ 4.25 Performance disclosures.

* * * * *

(a) * * *

(1) * * *

(ii) * * *

(H) Partially-funded accounts directed by a commodity trading advisor may be presented in accordance with § 4.35(a)(7).

* * * * *

■ 4. Section 4.35 is amended as follows:

■ a. By redesignating paragraphs (a)(7) and (a)(8) as (a)(8) and (a)(9) respectively;

■ b. And adding new paragraph (a)(7) to read as follows:

§ 4.35 Performance disclosures.

* * * * *

(a)(7) *Performance of partially-funded accounts.* Notwithstanding the foregoing, a commodity trading advisor will be deemed in compliance with this § 4.35(a) concerning the performance of partially-funded accounts if the commodity trading advisor presents the performance of such accounts in a manner that is balanced and is not in violation of the antifraud provisions of the Commodity Exchange Act or the Commission's regulations thereunder.

* * * * *

Issued in Washington, DC, on July 15, 2003 by the Commission.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 03–18413 Filed 7–18–03; 8:45 am]

BILLING CODE 6351–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

Oral Dosage Form New Animal Drugs; Meloxicam

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a new animal drug application (NADA) filed by Boehringer Ingelheim Vetmedica, Inc. The NADA provides for use of meloxicam oral suspension for the control of pain and inflammation associated with osteoarthritis in dogs.

DATES: This rule is effective July 21, 2003.

FOR FURTHER INFORMATION CONTACT: Melanie R. Berson, Center for Veterinary Medicine (HFV–110), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–7540, e-mail: mberson@cvm.fda.gov.

SUPPLEMENTARY INFORMATION: Boehringer Ingelheim Vetmedica, Inc., 2621 North Belt Highway, St. Joseph, MO 64506–2002, filed NADA 141–213 that provides for use of METACAM (meloxicam) Oral Suspension for the control of pain and inflammation associated with osteoarthritis in dogs. The NADA is approved as of April 15, 2003, and the regulations are amended in 21 CFR part 520 by adding new § 520.1350 to reflect the approval. The basis of approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 21 CFR part 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management

Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(c)(2)(F)(i)), this approval qualifies for 5 years of marketing exclusivity beginning April 15, 2003.

The agency has determined under 21 CFR 25.33(d)(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.

This rule does not meet the definition of ''rule'' in 5 U.S.C. 804(3)(A) because it is a rule of ''particular applicability.'' Therefore, it is not subject to the congressional review requirements in 5 U.S.C. 801–808.

List of Subjects in 21 CFR Part 520

Animal drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under the authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 520 is amended as follows:

PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS

■ 1. The authority citation for 21 CFR part 520 continues to read as follows:

Authority: 21 U.S.C. 360b.

■ 2. Section 520.1350 is added to read as follows:

§ 520.1350 Meloxicam.

(a) *Specifications.* Each milliliter of suspension contains 0.5 or 1.5 milligrams (mg) meloxicam.

(b) *Sponsor.* See No. 000010 in § 510.600(c) of this chapter for uses as in paragraph (c) of this section.

(c) *Conditions of use in dogs*—(1) *Amount.* Administer orally 0.2 mg/kilogram (kg) body weight on the first day of treatment. For all treatment after day 1, administer 0.1 mg/kg body weight once daily.

(2) *Indications for use.* For the control of pain and inflammation associated with osteoarthritis.

(3) *Limitations.* Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Dated: July 8, 2003.

Stephen F. Sundlof,

Director, Center for Veterinary Medicine.

[FR Doc. 03–18354 Filed 7–18–03; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

New Animal Drugs; Oxytetracycline Hydrochloride Soluble Powder

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental abbreviated new animal drug application (ANADA) filed by Cross Vetpharm Group Ltd. The supplemental ANADA provides for a new pouch size of oxytetracycline hydrochloride soluble powder used to make medicated drinking water for swine.

DATES: This rule is effective July 21, 2003.

FOR FURTHER INFORMATION CONTACT: Lonnie W. Luther, Center for Veterinary Medicine (HFV–104), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 301–827–8549, e-mail: *lluther@cvm.fda.gov.*

SUPPLEMENTARY INFORMATION: Cross Vetpharm Group Ltd., Broomhill Rd., Tallaght, Dublin 24, Ireland, filed a supplement to ANADA 200–144 that provides for a new pouch size of TETROXY (oxytetracycline HCl) Soluble Powder used to make medicated drinking water for administration to swine. The supplemental application is approved as of April 21, 2003, and the regulations are amended in 21 CFR 520.1660d to reflect the approval. The basis of approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 21 CFR 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

The agency has 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.

This rule does not meet the definition of ''rule'' in 5 U.S.C. 804(3)(A) because it is a rule of ''particular applicability.'' Therefore, it is not subject to the congressional review requirements in 5 U.S.C. 801–808.

List of Subjects in 21 CFR Part 520

Animal drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 520 is amended as follows:

PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS

■ 1. The authority citation for 21 CFR part 520 continues to read as follows:

Authority: 21 U.S.C. 360b.

§ 520.1660d [Amended]

■ 2. Section 520.1660d *Oxytetracycline hydrochloride soluble powder* is amended in paragraph (a)(9) by removing ''and 19.75 oz'' and by adding in its place '', 19.75 oz, and 3.91 lb''.

Dated: July 8, 2003.

Steven D. Vaughn,

Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 03–18351 Filed 7–18–03; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 522

Injectable or Implantable Dosage Form New Animal Drugs; Euthanasia Solution; Technical Amendment

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; technical amendment.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed by Schering-Plough Animal Health Corp. and a supplemental abbreviated new animal drug application (ANADA) filed by Delmarva Laboratories, Inc. The supplemental applications add environmental warning statements to product labeling.

DATES: This rule is effective July 21, 2003.

FOR FURTHER INFORMATION CONTACT: Mohammad I. Sharar, Center for Veterinary Medicine (HFV–216), Food and Drug Administration, 7500 Standish

CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Meloxicam Aurobindo 7.5 mg and 15 mg, tablets
Aurobindo Pharma B.V., the Netherlands

meloxicam

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 107063, 107068

10 January 2013

Pharmacotherapeutic group:	anti-inflammatory and antirheumatic products, non-steroids - oxicams
ATC code:	M01AC06
Route of administration:	oral
Therapeutic indication:	short-term symptomatic treatment of exacerbations of osteoarthritis; long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis
Prescription status:	prescription only
Date of authorisation in NL:	20 September 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Meloxicam Aurobindo 7.5 mg and 15 mg, tablets from Aurobindo Pharma B.V. The date of authorisation was on 20 September 2011 in the Netherlands.

The product is indicated for:

- short-term symptomatic treatment of exacerbations of osteoarthritis
- long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

A comprehensive description of the indications and posology is given in the SPC.

The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAIDs (including meloxicam): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

This national procedure concerns a generic application claiming essential similarity with the innovator products Movicox 7.5 mg and 15 mg, tablets (NL License RVG 19375-19376) which have been registered in the Netherlands by Boehringer Ingelheim B.V. since 9 January 1996.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the products is compared with the pharmacokinetic profile of the reference products Mobic 7.5 and 15 mg tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is meloxicam, an established active substance described in the European and British Pharmacopoeia (Ph.Eur., BP*). It is a pale yellow powder, which is soluble in N,N-dimethylformamide, very slightly soluble in ethanol and practically insoluble in water. Crystalline polymorph form I is used.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph for meloxicam and the additional CEP requirements. The specification is acceptable in view of the CEP and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six production-scale batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. and BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU or UK respectively.*

Medicinal Product

Composition
Meloxicam Aurobindo 7.5 and 15 mg tablets are light yellow, round, uncoated tablets with a score line between ‘F’ and ‘1’ or ‘2’ respectively debossed on one side and plain on the other side. The 15 mg tablet can be divided into equal halves.

The tablets are packed in white opaque PVC-PVdC/Aluminum blister packs.

The excipients are: lactose monohydrate, microcrystalline cellulose, sodium citrate, crospovidone, povidone, colloidal anhydrous silica and magnesium stearate.

The tablets are not dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of the excipients is justified and their functions explained. Optimum amounts of the pharmaceutically active excipients have been established. The score lines of both tablets comply with the requirements of the Ph. Eur. However, the SPC states that only the 15 mg tablet can be divided into equal halves. Breakability tests with the 7.5 mg and the 15 mg tablets demonstrated that the tablets comply with the Ph. Eur. requirement for uniformity of mass of subdivided tablets. The use of the UK reference products in the bioequivalence studies has been justified. Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products. The test products are acceptable.

Manufacturing process

The manufacturing process for meloxicam 7.5 and 15 mg tablets consists of the following steps: sifting, dry mixing, preparation of the binder solution, granulation, drying, sifting and milling, sifting, blending and lubrication and compression and packing. Adequate in-process controls have been set.
The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data on the products have been presented for two small scale batches of both strengths. Full scale validation will be conducted post-approval. The product is manufactured using standard, conventional manufacturing techniques. In view of that, this approach is acceptable.

Control of excipients

The excipients comply with the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. and USP. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identity (by TLC and HPLC), average weight, dissolution, assay, related substances, uniformity of dosage units and microbial contamination. The release and shelf-life requirements are identical and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from two small scale batches for both strengths have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for two small-scale production batches, stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed blister packaging. No significant changes in the drug product were observed after 6 months of accelerated and 24 months of long-term stability study for meloxicam 7.5 mg and 15 mg tablets. It demonstrated that the tablets are not sensitive to light. Based on the data provided, a shelf life of 2 years was granted. No additional storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only lactose is of animal origin. The lactose used comes from milk for human consumption and does not present any risk of TSE contamination. A declaration on its TSE safety was provided.

II.2 Non-clinical aspects

This product is a generic formulation of Movicox, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of meloxicam released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Meloxicam is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Meloxicam Aurobindo 7.5 mg and 15 mg tablets (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference products Mobic 7.5 mg and 15 mg tablets (Boehringer Ingelheim, UK).

The choice of the reference products
The choice of the reference products in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 7.5 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 19-36 years. Each subject received a single dose (7.5 mg) of one of the 2 meloxicam formulations. The tablet was orally administered after an overnight fast of 10 hours with 240 ml water 30 minutes after a high caloric, high fat meal (985 kCal). There were 2 dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 120.0 hours after administration of the products. The overall study design is considered acceptable considering the absorption rate and half-life.
Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject did not show up in the second period. The dropout was not included in the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of meloxicam under fed conditions.

Treatment N=27	**AUC_{0-t}** ug.h/ml	**$AUC_{0-\infty}$** ug.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	29.52 ± 13.48	32.35 ± 15.60	1.05 ± 0.25	4.5 1.0 – 7.0	24 ± 9
Reference	31.37 ± 14.33	33.84 ± 16.12	1.05 ± 0.27	4.5 3.0 – 6.5	25 ± 9
***Ratio (90% CI)**	0.95 (0.91 – 0.98)	0.96 (0.93 – 0.99)	1.00 (0.95 – 1.06)	--	--
CV (%)	8	8	13	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of meloxicam under fasted conditions, it can be concluded that Meloxicam Aurobindo 7.5 mg and Mobic 7.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
The formulations were well tolerated, only three adverse events were reported.

Bioequivalence study II – 15 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 26 healthy male subjects, aged 18-41 years. Each subject received a single dose (15 mg) of one of the 2 meloxicam formulations. The tablet was orally administered after an overnight fast of 10 hours with 240 ml water during a high caloric, high fat meal (985 kCal). There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 120.0 hours after administration of the products. The overall study design is considered acceptable considering the absorption rate and half-life.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject did not show up in the second period, and one subject vomited after the first dose. Both subjects were withdrawn from the study. The dropouts were not included in the statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of meloxicam under fed conditions.

Treatment N=27	**AUC_{0-t}** ug.h/ml	**$AUC_{0-\infty}$** ug.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	37.54 ± 15.48	40.72 ± 19.12	1.16 ± 0.21	4.5 1.5 – 16.0	25 ± 10
Reference	37.67 ± 15.00	41.48 ± 19.06	1.05 ± 0.18	6.5 4.5 – 12.0	26 ± 11
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	0.99 (0.94 – 1.04)	1.10 (1.05 – 1.15)	--	--
CV (%)	10	9.9	9	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the

pharmacokinetic parameters of meloxicam under fasted conditions, it can be concluded that Meloxicam Aurobindo 15 mg and Mobic 15 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
The formulations were well tolerated. Three adverse events were reported during the entire duration of the study, all adverse events were post study lab abnormalities.

As meloxicam should be taken with food, as described in the SPC, a study under fed conditions with a high fat, high caloric meal is justified according the new guideline on Bioequivalence.
The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Meloxicam was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of meloxicam can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Movicox tablets.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report was provided. Reference is made to the successfully user tested PIL for another meloxicam 7.5 mg/15 mg product. Both PILs contain the same information for the sections ‘indications’, ‘contra-indications’, ‘warnings’, ‘other safety information’ and ‘side-effects’. Layout and design of the two PILs are also the same (in-house style). The bridging report was accepted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Meloxicam Aurobindo 7.5 mg and 15 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Movicox 7.5 mg and 15 mg tablets. Movicox is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence of both tablet formulations has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other meloxicam containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Meloxicam Aurobindo 7.5 mg and 15 mg, tablets were authorised in the Netherlands on 20 September 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of the marketing authorisation.	--	MA transfer	17-10-2011	15-11-2011	Approval	N

Appendix 12

US006869948B1

(12) **United States Patent**
Bock et al.

(10) **Patent No.: US 6,869,948 B1**
(45) **Date of Patent: Mar. 22, 2005**

(54) **MELOXICAM FOR ORAL ADMINISTRATION**

(75) Inventors: **Thomas Bock**, Biberach (DE); **Paul Saegmueller**, Bergatreute (DE); **Peter Sieger**, Mittelbiberach (DE); **Dietrich Tuerck**, Ulm (DE)

(73) Assignee: **Boehringer Ingelheim Pharma KG**, Ingelheim (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 554 days.

(21) Appl. No.: **09/277,049**

(22) Filed: **Mar. 26, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/088,850, filed on Jun. 10, 1998.

(30) **Foreign Application Priority Data**

Mar. 27, 1998 (EP) 98105569

(51) **Int. Cl.**[7] **A61K 31/54**; C07D 279/16
(52) **U.S. Cl.** **514/226.5**; 544/49
(58) **Field of Search** 544/49; 514/226.5

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,233,299 A 11/1980 Trummlitz et al.
4,748,174 A 5/1988 Veronesi

FOREIGN PATENT DOCUMENTS

DE	37 00 172 A	7/1987
EP	0 002 482 A	6/1979
WO	WO 97 17978 A	5/1997
WO	WO 99 09988 A	3/1999

OTHER PUBLICATIONS

Luger et al; "Structure and physicochemical properties of meloxicam, a new NSAID"; European Journal of Pharmaceutical Sciences; Bd. 4, 1996, Seiten 175–187, XP002074736 *siehe Zusammenfassung; Seite 177, linke Spalte; und Seite 178 Tabelle 1*.

Primary Examiner—Richard L. Raymond
Assistant Examiner—Tamthom N. Truong
(74) *Attorney, Agent, or Firm*—Robert P. Raymond; Timothy X. Witkowski; Anthony P. Bottino

(57) **ABSTRACT**

The invention relates in its first aspect to a rapidly decomposing tablet for pain therapy containing meloxicam [4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] in the form of a salt with an inorganic or organic base providing rapid absorption of the active substance, the process of its preparation by direct tabletting, and furthermore relates in a second aspect to the crystalline meloxicam meglumin salt mono- and dihydrate and the preparation thereof.

18 Claims, 9 Drawing Sheets

Appendix 12

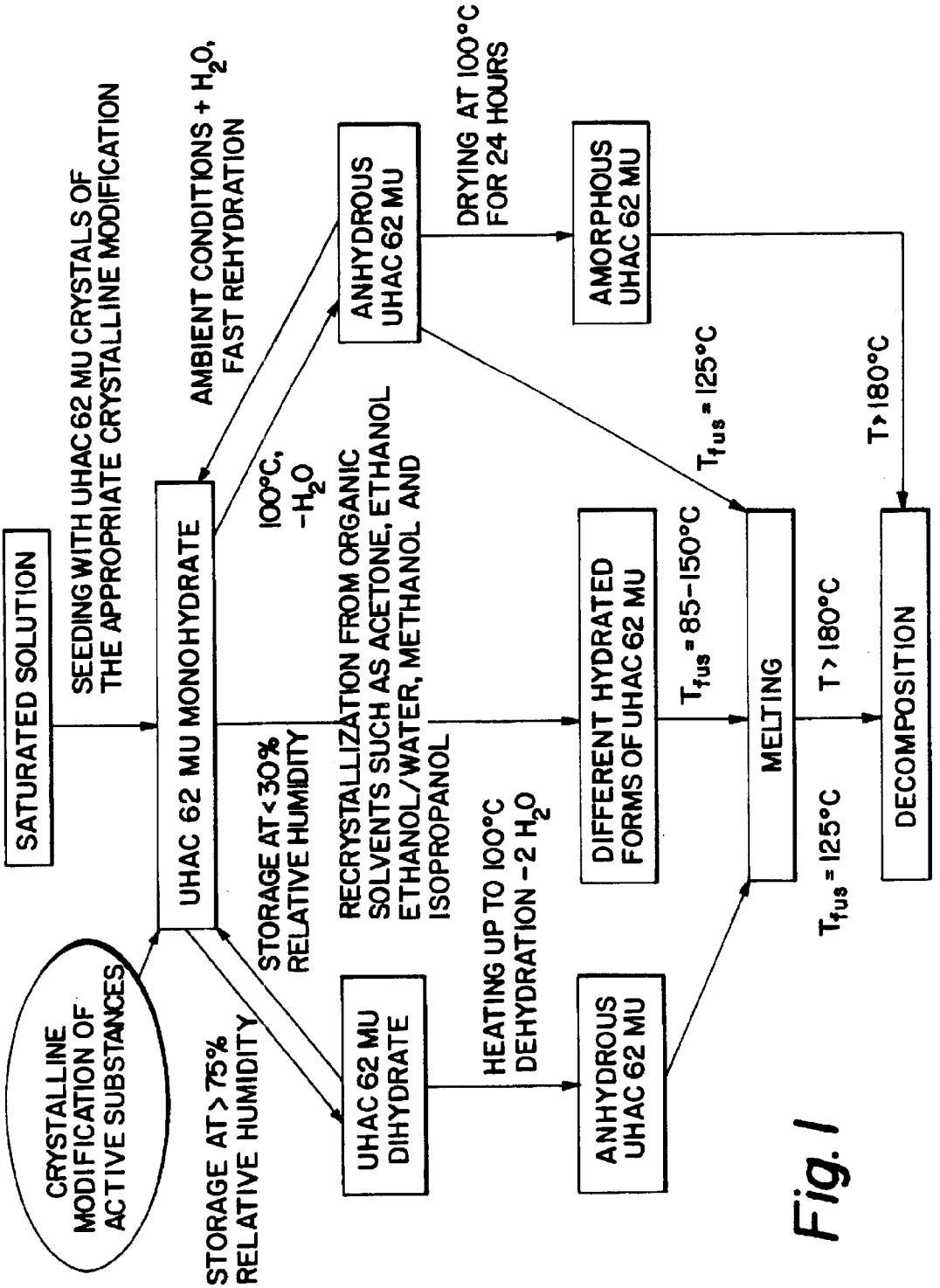


Fig. 1

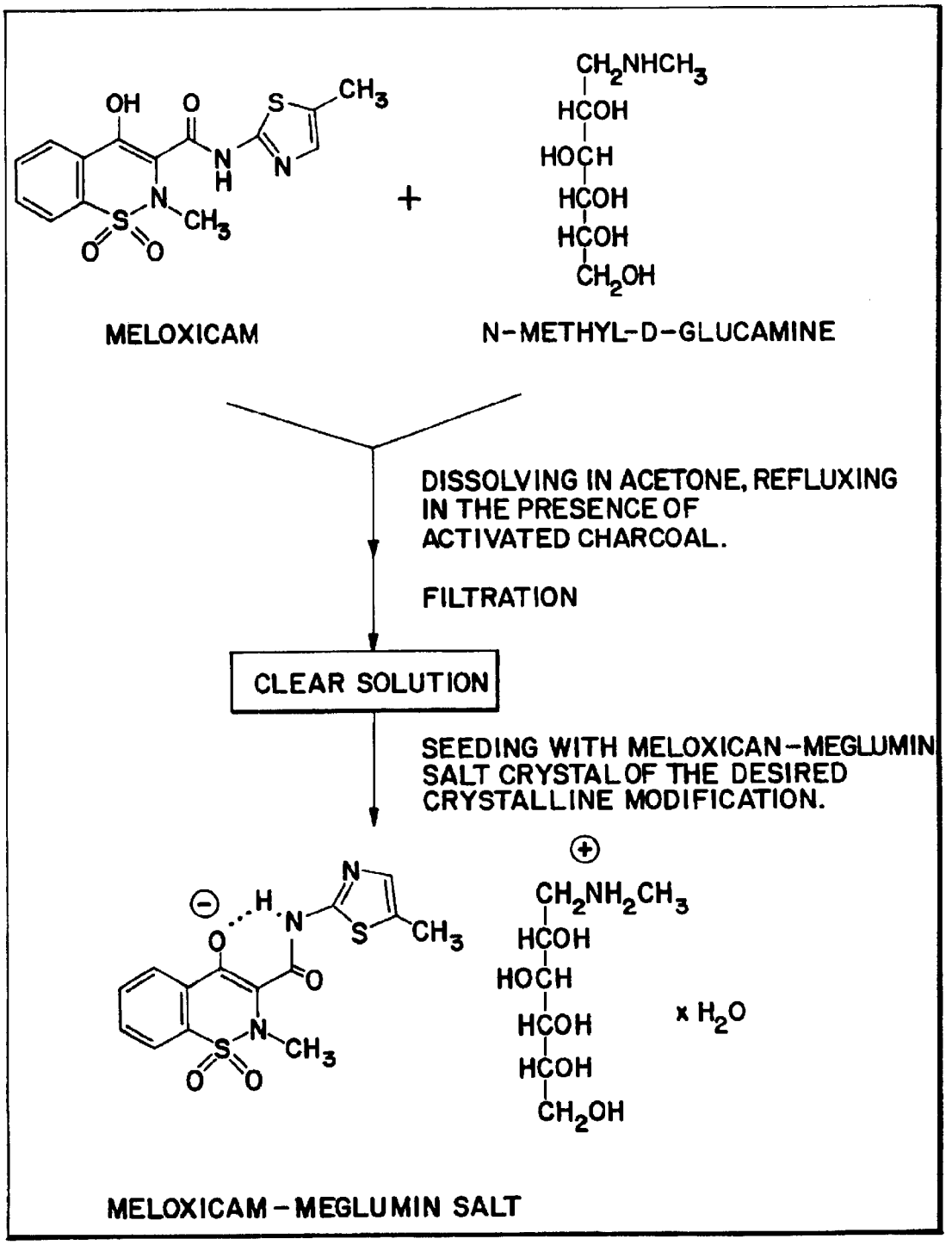

MELOXICAM
N-METHYL-D-GLUCAMINE
DISSOLVING IN ACETONE, REFLUXING IN THE PRESENCE OF ACTIVATED CHARCOAL.
FILTRATION
CLEAR SOLUTION
SEEDING WITH MELOXICAN-MEGLUMIN SALT CRYSTAL OF THE DESIRED CRYSTALLINE MODIFICATION.
x H2O
MELOXICAM-MEGLUMIN SALT

Fig. 2

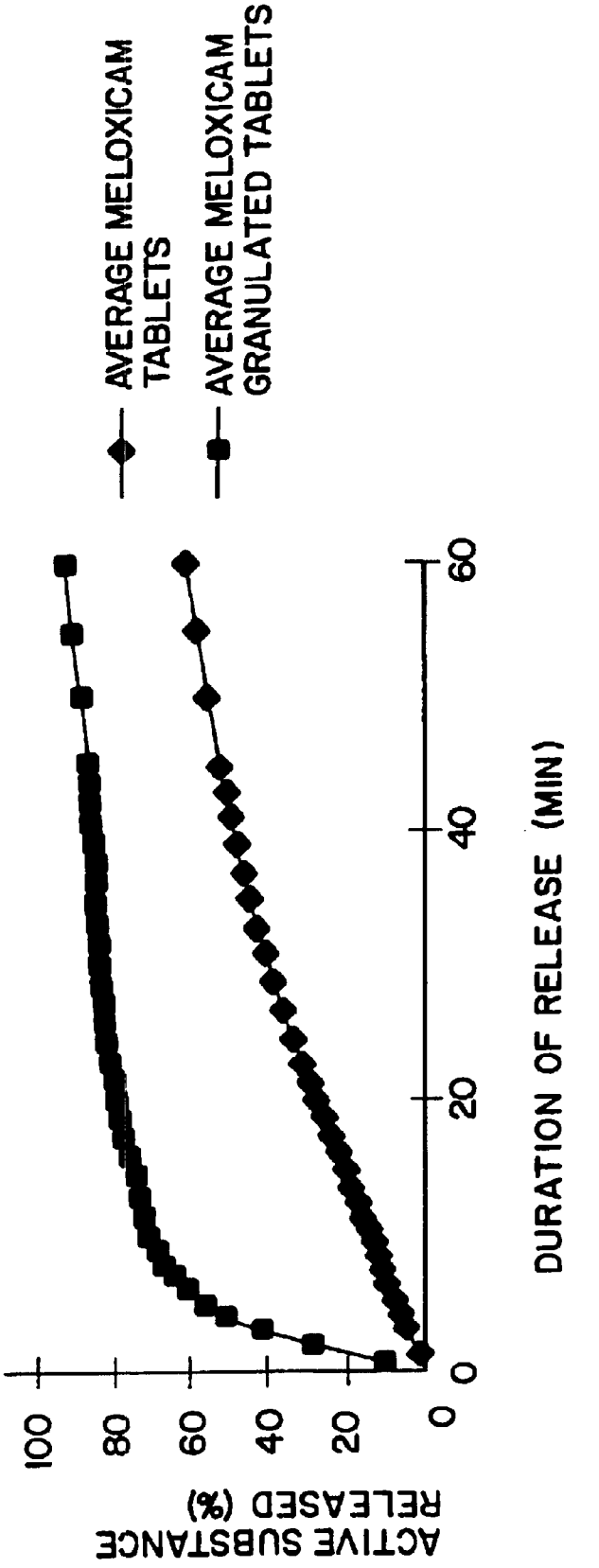

AVERAGE MELOXICAM TABLETS
AVERAGE MELOXICAM GRANULATED TABLETS
ACTIVE SUBSTANCE RELEASED (%)
0
20
40
60
80
100
0
20
40
60
DURATION OF RELEASE (MIN)

Fig. 3

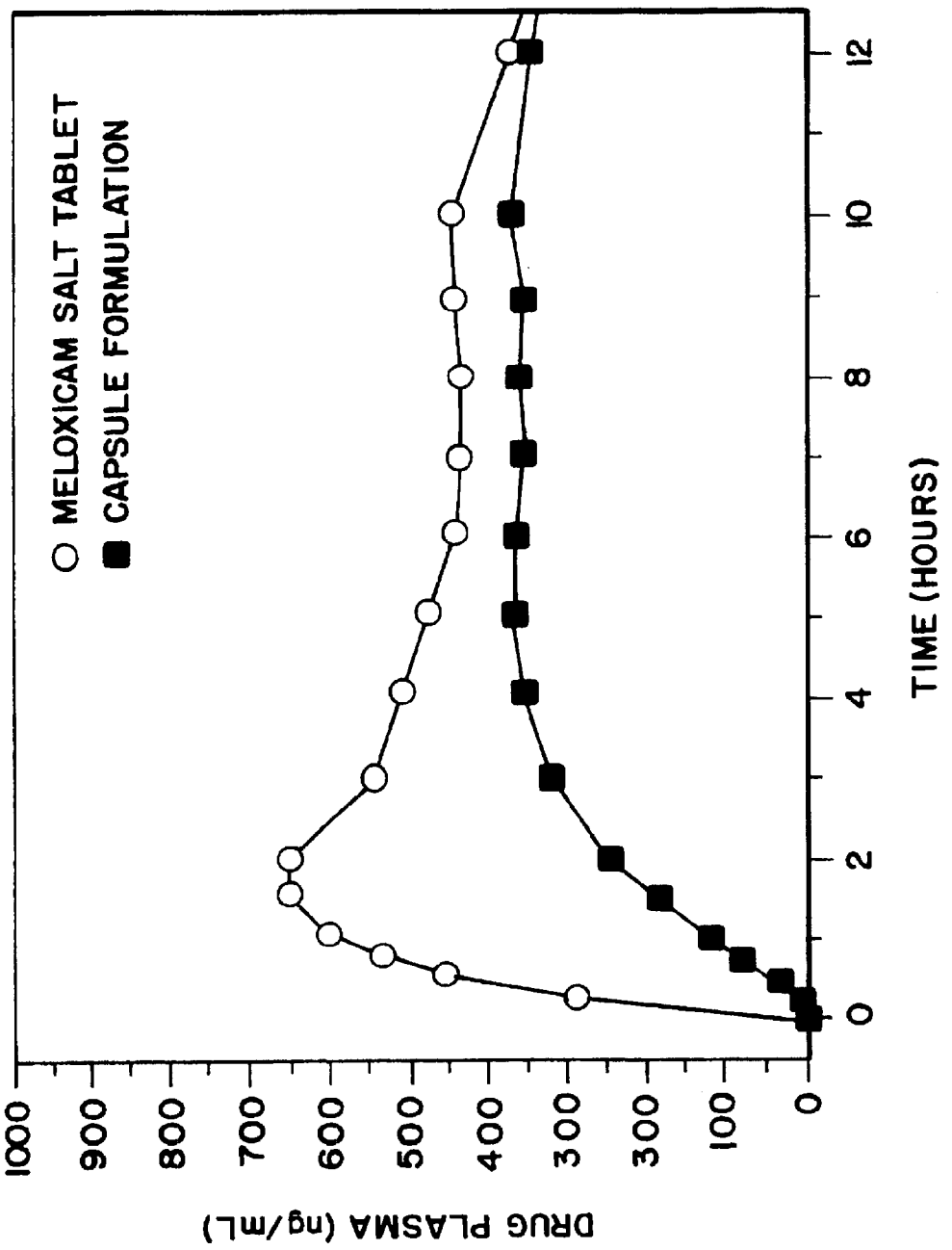

MELOXICAM SALT TABLET
CAPSULE FORMULATION
DRUG PLASMA (ng/mL)
1000
900
800
700
600
500
400
300
300
100
0
0
2
4
6
8
10
12
TIME (HOURS)

Fig. 4

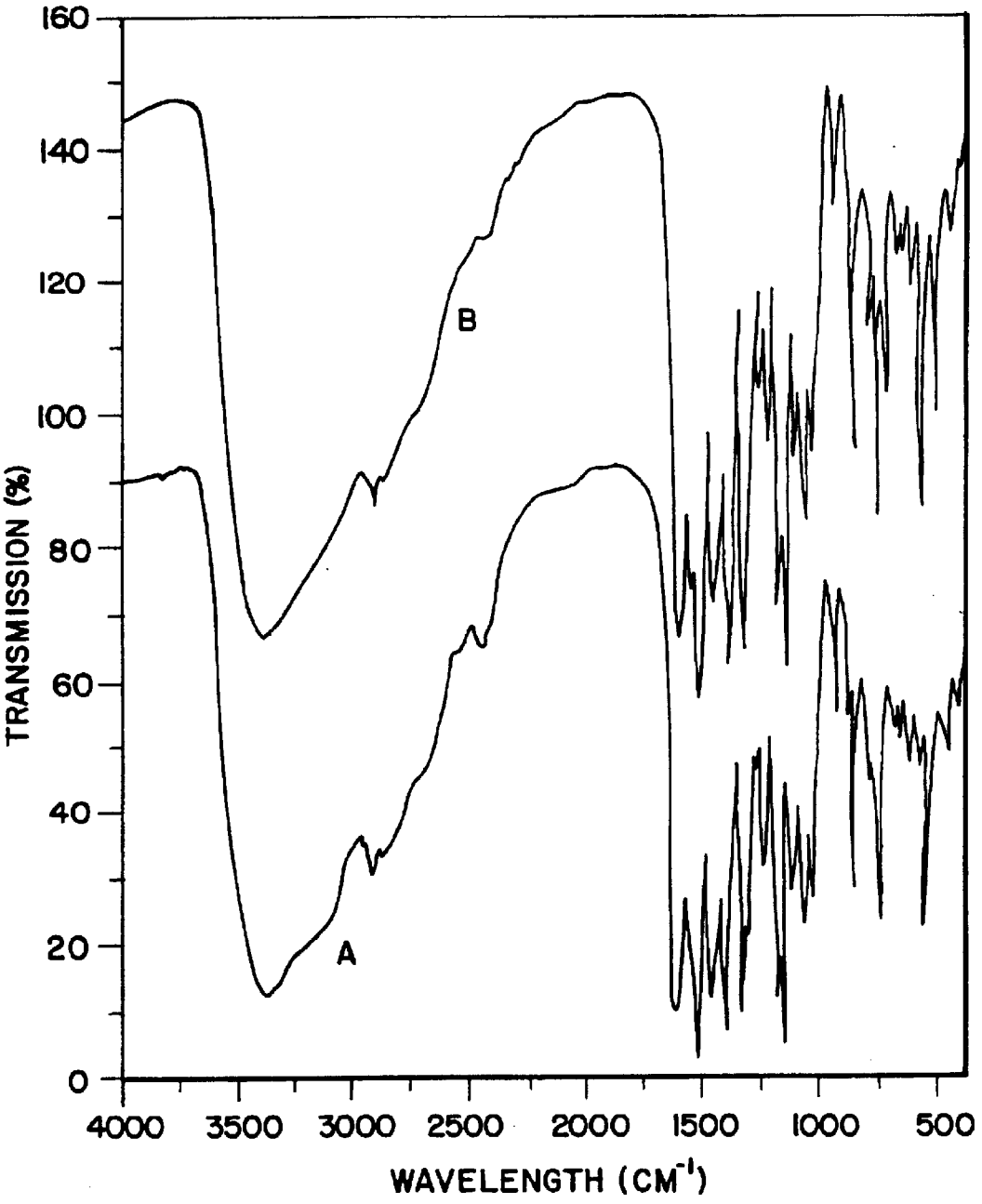

160
140
120
100
80
60
40
20
0
TRANSMISSION (%)
B
A
4000
3500
3000
2500
2000
1500
1000
500
WAVELENGTH (CM-1)

Fig. 5

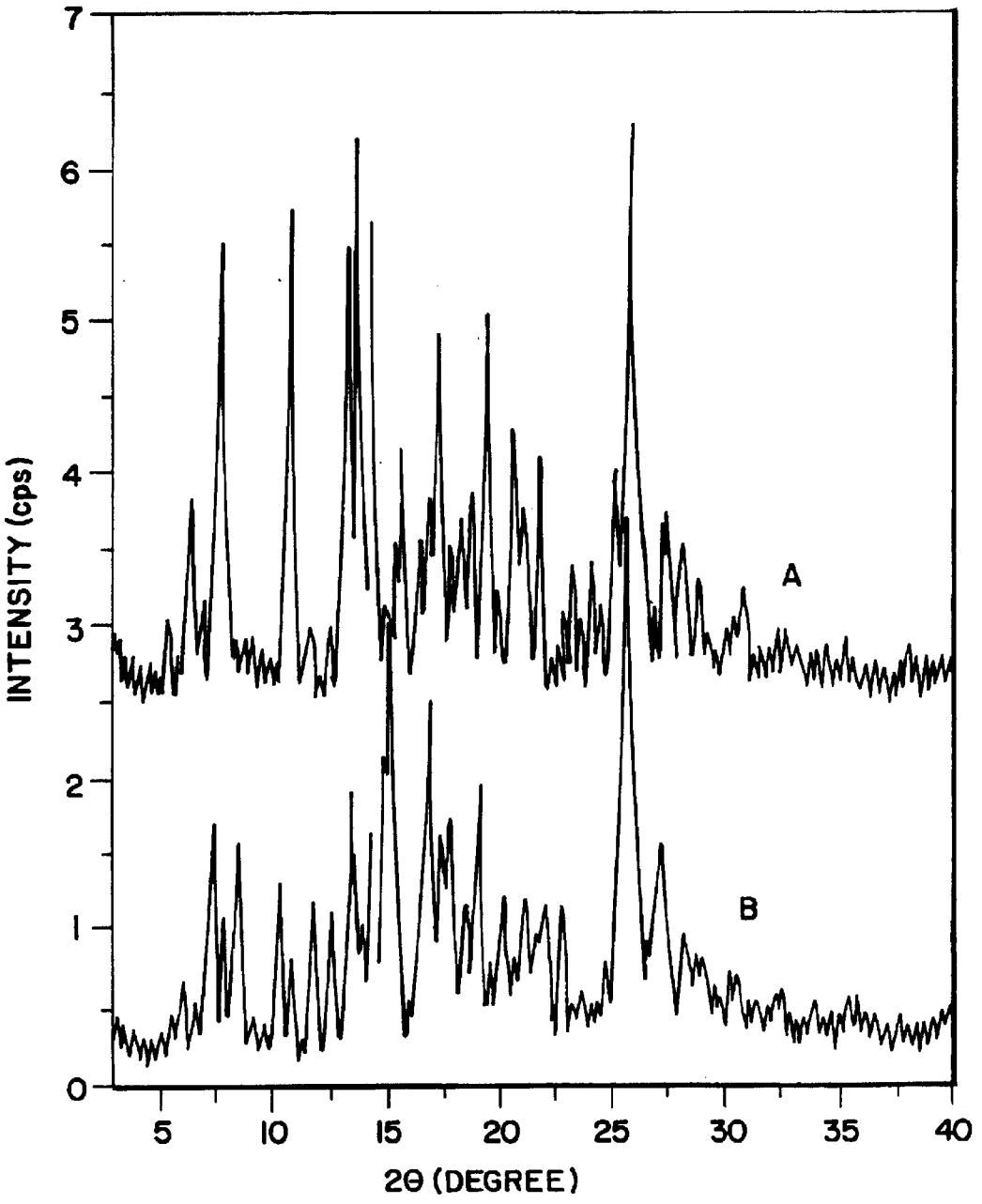


Fig. 6

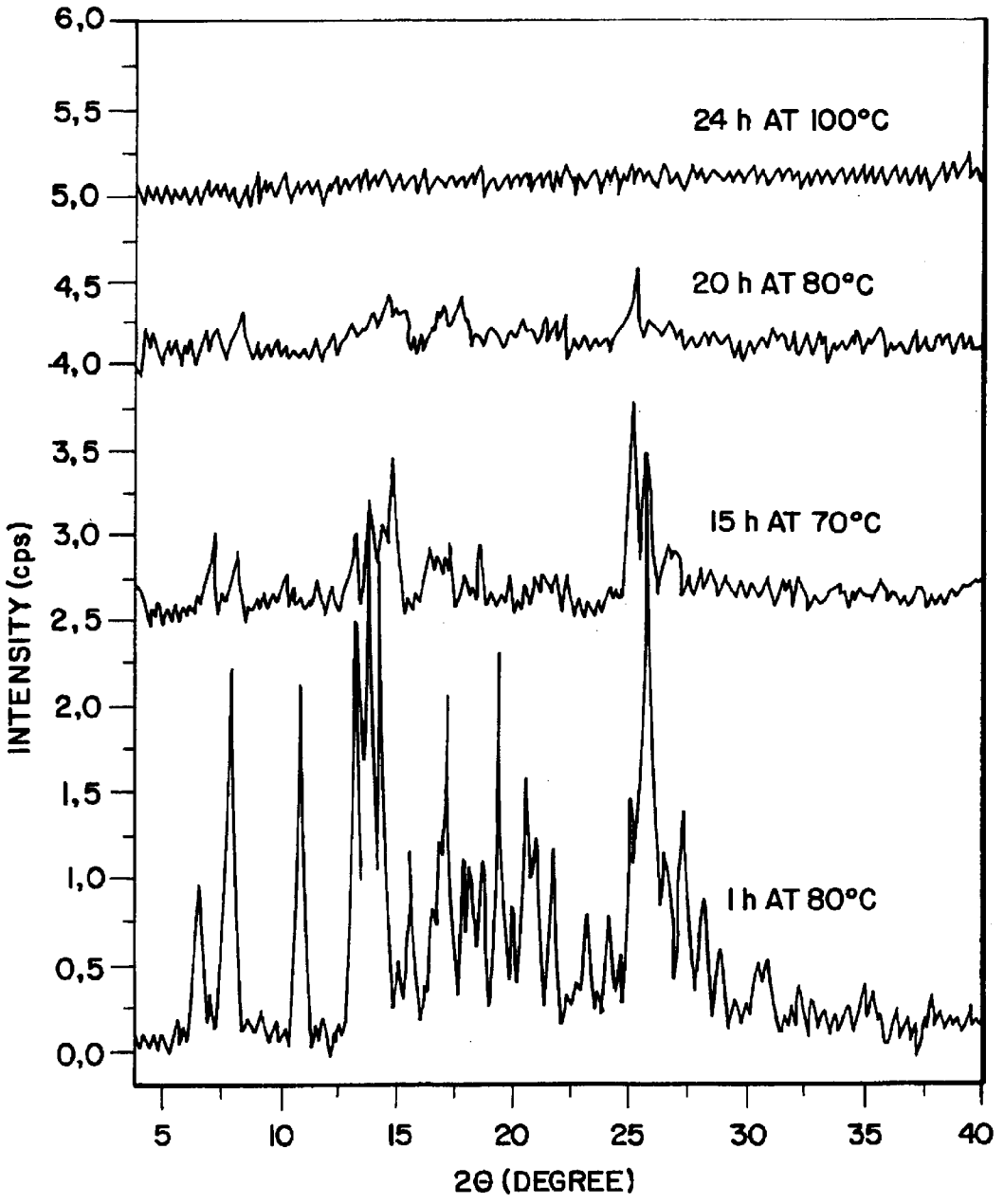

6,0
5,5
5,0
4,5
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
INTENSITY (cps)
24 h AT 100°C
20 h AT 80°C
15 h AT 70°C
1 h AT 80°C
5
10
15
20
25
30
35
40
2θ (DEGREE)

Fig. 7

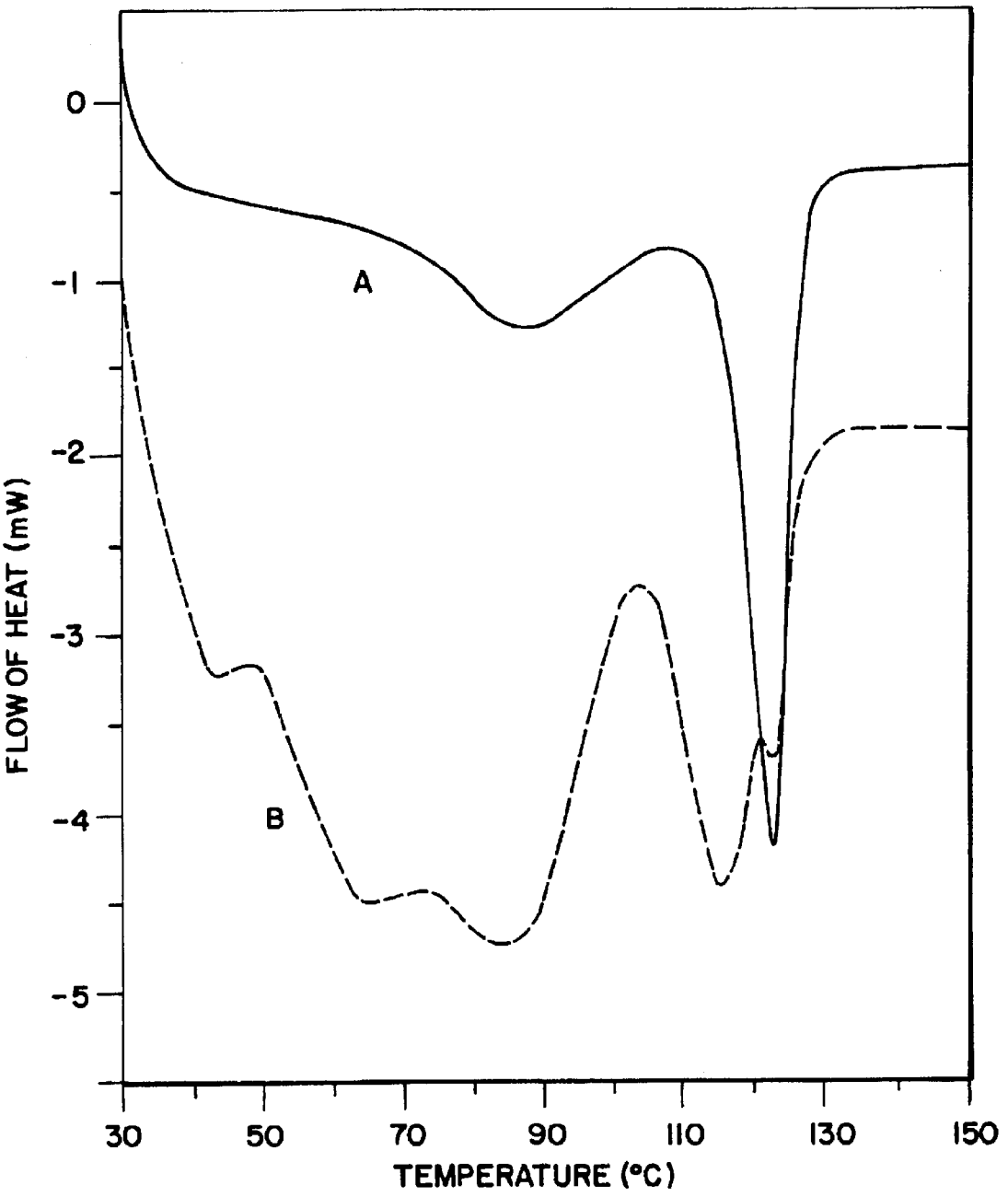


Fig. 8

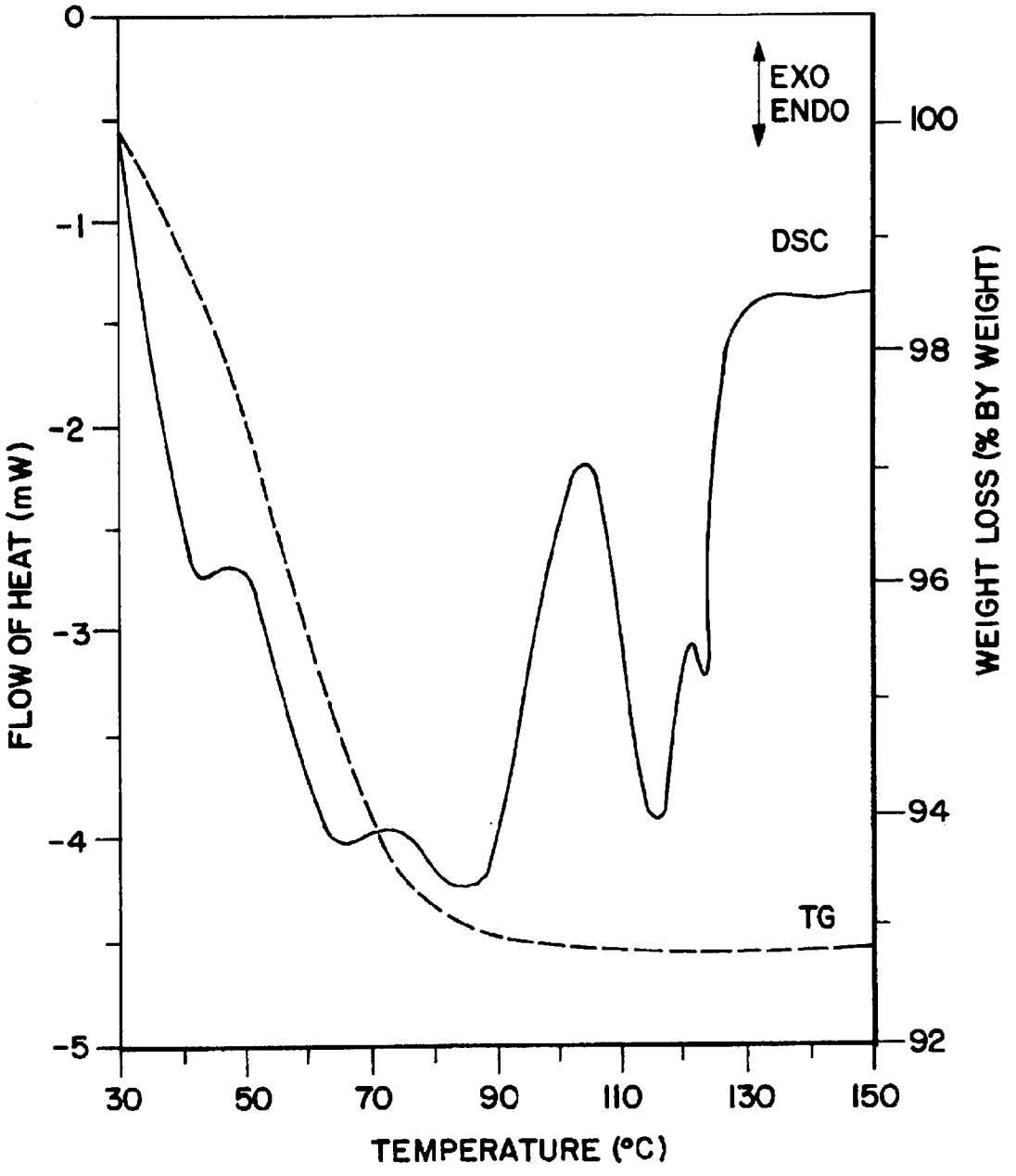

0
-1
-2
-3
-4
-5
FLOW OF HEAT (mW)
EXO
ENDO
DSC
TG
100
98
96
94
92
WEIGHT LOSS (% BY WEIGHT)
30
50
70
90
110
130
150
TEMPERATURE (°C)

Fig. 9

MELOXICAM FOR ORAL ADMINISTRATION

RELATED APPLICATIONS

The benefit of prior provisional application Ser. No. 60/088,850, filed on Jun. 10, 1998, is hereby claimed.

TECHNICAL FIELD OF THE INVENTION

The invention relates to new pharmaceutical compositions for the oral administration of the NSAID (nonsteroidal-anti-inflammatory drug) meloxicam.

BACKGROUND OF THE INVENTION

The drugs used for the treatment of rheumatic diseases often have antiphlogistic as well as analgesic properties. For this reason they are used not only to treat chronic rheumatic diseases but also for acute rheumatic attacks and for acute pain treatment.

Many of these pharmaceutical compositions have only limited solubility and for this reason are absorbed only slowly by the body. In the treatment of acute pain, a rapid influx of active substance is essential to ensure that the activity sets in rapidly. It is therefore often necessary to increase the speed of dissolution and solubility of the active substances in question.

For known drugs in this field, different approaches have been adopted, e.g. ibuprofen and diclofenac are used in the form of their salts or piroxicam is used in the form of β-cyclodextrin inclusion compounds. However, when administered by oral route, these active substances do not always exhibit a sufficient plasma concentration for rapid effect within a short time. The pharmacokinetic differences of ibuprofen-lysinate compared with ibuprofenic acid are described for example in Int. J. Clin. Pharmacol., Ther. Toxicol. ,Vol. 27, No. 7, 324–328 (1989). It says that the average peak-plasma level measured on 8 fasting test subjects in the case of ibuprofen-lysinate (1000 mg, film-coated tablet) was achieved on average 0.55 h after administration and was 69.1: g/ml, whereas the corresponding values for ibuprofenic acid (600 mg, sugar-coated tablet) are given as 0.89 h and 50.8: g/ml. In non-fasting test subjects the differences lose statistical significance according to the authors and amount to 50.3: g/ml ibuprofen-lysinate after 1.18 h and 44.6 g/ml for ibuprofenic acid after 1.55 h. DE 37 00 172 explains that numerous NSAID's do not dissolve easily in water and are therefore not really suitable for preparing parenteral formulations. To overcome this problem, the use of N-(methyl)-glucamine and glucamine salts of a number of NSAIDs, including, inter alia, Isoxicam, Tenoxicam and Piroxicam has been proposed. A parenteral Piroxicam-N-(methyl)-glucamine formulation is described as Example 4. It is also stated that these salts can also be administered in oral, rectal or topical formulations, but the published application contains no information on the absorption of oral formulations. The problem described therein, namely the preparation of a parenteral aqueous formulation of a comparatively insoluble active substance, differs substantially from the objective of the present invention. As explained hereinafter, this consists in providing an orally administered solid pharmaceutical preparation of meloxicam which produces effective plasma levels soon after administration. In addition, the starting point of the present invention was considerably more difficult, as free meloxicam is less water-soluble, by a factor of about 10, than free piroxicam over a wide pH range (European Journal of Pharmaceutical Science 4 (1996), 175–187, particularly FIG. 10 on page 184).

Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is an antirheumatic which is distinguished by the fact that it is well tolerated by the stomach at the doses necessary for therapy. The active substance and its sodium salt—as well as its N-methyl-D-glucamine salt (meglumin salt) are described in EP-A-0 002 482. The anti-inflammatory and pain-relieving properties of meloxicam also make this active substance very interesting for use in pain therapy. However, the active substance has very low solubility in the acid range which prevails in the upper part of the gastrointestinal channel. It is therefore absorbed with a time delay after administration. Maximum plasma levels are reached within 2–8 hours, depending on the formulation. However, the activity is long-lasting and highly effective. As a rule, therefore, a single dose each day is sufficient. In order to open up this active substance, which is suitable for pain therapy, for treating acute conditions as well, it is necessary to ensure rapid absorption and, at the same time, a rapid onset of activity.

DESCRIPTION OF THE INVENTION

The object of the present invention is to provide a solid pharmaceutical preparation of meloxicam, suitable for oral administration, from which the active substance is released and absorbed rapidly, so that a plasma level suitable for treating acute pain can be achieved sufficiently rapidly. The following profile of requirements can be defined in connection with this.

The maximum plasma level C_{max} should be higher than after the administration of an equal dose of a conventional meloxicam capsule formulation and should be achieved very much sooner. A high enough effective plasma level should then be maintained for a certain length of time. In particular, C_{max} should be reached at the latest two hours after the administration of a single dose and should be at a dosage of 7.5 mg in the range from 650 to 1000 ng/ml. Ideally C_{max} at this dosage should correspond to about twice the maximum plasma level which is achieved with the conventional 7.5 mg capsule formulation and should therefore be in the range from 800 to 900 ng/mL. After the maximum plasma level is exceeded, a plasma level of 500 to 700 ng/ml should be maintained for 1 to 3 hours, but ideally a plasma level of 550 to 650 ng/ml, which corresponds to the steady state average plasma levels of about 600 ng/ml after the administration of the conventional 7.5 mg capsules. Moreover, the total absorption of the formulation according to the invention and the conventional capsule formulation with the same dose should be equivalent.

Meloxicam is capable of forming salts with inorganic bases, e.g. the sodium, potassium or ammonium salt, and also with organic bases, e.g. the meglumin salt, the Tris salt (Tris-(hydroxymethyl)aminomethane) or salts with basic amino acids such as L-lysine or L-arginine. In connection with the objective of the invention the solubilities of the active substance and its salts are of interest.

TABLE 1

Saturation solubility of meloxicam and its salts in various dissolving media

	Solubility at ambient temperature [mg/100 ml]			
Medium	Melox-icam	Sodium salt	ammonium salt	meglumin salt
0.1 N hydrochloric acid (pH 1)	0.09	0.05	0.04	0.1
Buffer pH 4	0.05	0.02	0.02	0.04
Water (pH 7)	0.2	785	230	860
Buffer pH 7.4	About 100	635	285	1290

TABLE 1-continued

Saturation solubility of meloxicam and its salts in various dissolving media

Medium	Solubility at ambient temperature [mg/100 ml] Melox-icam	Sodium salt	ammonium salt	meglumin salt
Buffer pH 10	231	1215	440	2315
0.1 N sodium hydroxide solution (pH 13)	2570	1215	1960	2900

The data in Table 1 show the following:

Both meloxicam and meloxicam salts are only poorly soluble in aqueous systems at pH values≦4, with no apparent significant differences in the solubility of the different compounds. As the pH increases to between 4 and 10 the solubility of the meloxicam salts increases, particularly the sodium and meglumin salt, significantly more than that of the free meloxicam, and at very high pH values the effect of the increased solubility levels out. The free meloxicam exhibits a substantial increase in solubility only at pH levels above 7. At pH 13 meloxicam and its salts no longer exhibit any substantial differences in solubility. Accordingly, elevated dissolution rates can theoretically be expected for meloxicam salts at pH values above 4, and for free meloxicam only at pH values above 7.

It is known that the pH value of gastric juices can vary between 1 and 6 in fasting patients and is usually between 3 and 5 in non-fasting patients.

Since meloxicam salts with bases in the acidic pH range which prevails in the stomach have very low solubility, one might expect that a solid meloxicam salt in this environment would dissolve only very slowly and thus be available for resorption or that a corresponding meloxicam salt already dissolved would be precipitated in this environment. An essential difference in resorption characteristics would not be expected between meloxicam and its salts under these conditions on the basis of the solubility data. On the other hand, one would expect salts of meloxicam with bases in a less acidic medium of the small intestine to dissolve faster and to a greater degree than free meloxicam and be absorbed there correspondingly faster than the free meloxicam. The release and resorption of the active substance only in the small intestine, whilst the active substance might be protected by a gastric juice-resistant coating during its passage through the stomach, is not however suitable as a solution to the problem of the invention. The passage through the stomach after a pharmaceutical preparation has been administered takes too long, with the result that acute pain is not treated rapidly enough. Moreover, the time taken for the effect to set in would depend to a considerable extent on what had been eaten and would thus be subject to individual fluctuations.

When choosing a suitable form of active substance for developing a formulation capable of solving the problem of the invention, it is necessary to take account not only of the pH-dependent solubilities but also other physicochemical properties of meloxicam and its salts. Polymorphism of the active component, possibly the presence of various crystalline, variously solvated or amorphous modifications, can have a considerable influence on the chemical, biological and pharmaceutical properties of a drug. The meloxicam meglumin salt shows a strong tendency to form various polymorphic forms and crystallises out of various organic solvents, e.g. acetone, methanol, ethanol, ethanol/water (8:2, v/v) and isopropanol, in various crystalline modifications which contain 4–5% water of hydration, as can be shown by microscopic, IR-spectroscopic and thermal analysis as well as X-ray powder diffractometry. FIG. **1** shows an overview of the polymorphism present. Moreover, the meloxicam-meglumin salt displays only a slight tendency to spontaneous crystallisation.

The crystalline monohydrate modification of the meloxicam-meglumin salt is hygroscopic, whereas the meloxicam-sodium salt has no hygroscopic properties. Under ambient conditions the monohydrate of the meloxicam-meglumin salt is the stable modification, but at a relative humidity of over 75% a dihydrate is formed. The enclosed water can only be eliminated from the dihydrate under conditions of very great dryness. However, after dehydration, no stable anhydrous modification is obtained, but the anhydrous form very rapidly absorbs water to form the monohydrate form which is stable under ambient conditions. The water absorption/desorption characteristics of meloxicam-meglumin exhibit a hysteresis effect. By intensive drying over a fairly long period the anhydrous form changes more and more into an amorphous form and after 24 h at 100° C. the material is totally amorphous.

In particular, the polymorphism and hygroscopic nature of the meloxicam-meglumin salt led us to expect considerable problems for the use of this form of active substance in a pharmaceutical formulation, as only a uniform, stable modification capable of being manufactured reproducibly can be used.

The meloxicam-meglumin salt which is primarily obtained according to Example 3 of EP-A-0 002 482 is anhydrous and amorphous (drying at 80° over phosphorus pentoxide). This modification is certainly suitable for the preparation of parenteral formulations but not for the preparation of solid pharmaceutical preparations as this form does not satisfy the criteria specified above, but changes into a hydrated form when stored under normal ambient conditions.

Surprisingly, it has been found that meloxicam from the salts formed with bases becomes available for absorption substantially faster after adimninistration and in greater quantities than neutral meloxicam in spite of the low solubility at low pH levels which correspond to the environment of the stomach. The rise in the plasma levels after oral administration of the salts of meloxicam takes place considerably faster than when pure meloxicam is used. The high degree and rapidity of the rise in plasma levels which can be achieved with meloxicam salts, particularly the meloxicam-meglumin salt, could not have been expected by anyone skilled in the art, taking into account the properties of the NSAID salts known from the prior art. The increased solubility obtained by using a meloxicam salt surprisingly occurs in vivo even at low pH values. This makes it possible for large amounts of the active substance to be dissolved even immediately after administration and thus become available for absorption by the body.

Example 7 together with FIG. **4** shows that after oral administration of a meloxicam salt formulation the plasma level rises considerably faster than after the administration of a conventional capsule formulation of the neutral active substance. Just 15 min after administration of the meloxicam-meglumin salt formulation according to the invention, a plasma level of 286 ng/ml is achieved, which virtually corresponds to the minimum plasma concentration in the steady-state, whilst 30 min after administration of the

comparative formulation, still no appreciable plasma level (42 ng/ml) can be detected. Moreover, with the formulation according to the invention, after barely 2 hours a maximum plasma level of 812 ng/ml is obtained, which is twice as great as the minimum steady-state plasma level achieved with the comparative formulation (the maximum plasma level was determined on the basis of variability in time, not from the average curve in FIG. **4**, but from the underlying individual curves). Thus, a rapid onset of activity as well as a particularly high activity can be expected in the first 2–3 hours after taking a formulation according to the invention, particularly a meloxicam-meglumin salt formulation, which is important for relieving acute pain. With the comparative formulation, on the other hand, no marked plasma level peak is achieved, but rather the plasma level rises more or less continuously until it reaches a plateau in the steady state.

The AUC0-∞ (AUC: area under the plasma concentration-time curve, 0-∞: from time 0 of the administration to infinity; measurement of resorption) of the conventional capsule formulation according to FIG. **4** is 14.1 μg h/mL, that of the meloxicam-meglumin salt formulation is 15.0 μg h/mL; the two are to be regarded as equivalent with regard to this parameter.

Other approaches to solving the problem of the present invention, e.g. the formation of inclusion compounds of meloxicam with β-cyclodextrin, did not produce sufficiently high plasma concentrations within a short period. Similarly, compression of a mixture of the two individual components meloxicam and meglumin did not solve the problem of the present invention.

The invention therefore relates to the use of a meloxicam salt of an inorganic or organic base for preparing an orally administered solid drug preparation from which the active substance is rapidly released and absorbed, for pain therapy, particularly for treating acute rheumatic attacks and for fighting acute pain. Suitable salts include, for example, the sodium, potassium or ammonium salt, the meglumin salt, the Tris salt or the salt of a basic amino acid such as L-lysine or L-arginine. The meloxicam-meglumin salt and the meloxicam sodium salt are preferred, the meloxicam-meglumin salt is particularly preferred, e.g. the meloxicam-meglumin salt dihydrate or especially the meloxicam-meglumin salt monohydrate.

In order to ensure rapid release of active substance after oral administration, it is also advantageous if the pharmaceutical preparation has a very short decomposition time, since as a rule the release of active substance can only proceed to a greater extent after breakdown. It has been found that a sufficiently short breakdown time can be achieved if the active substance is made into tablets directly with suitable excipients such as lactose, dicalcium phosphate, cellulose and suitable breakdown adjuvants such as crosslinked polyvinylpyrrolidone or sodium starch, i.e. the corresponding powder mixtures are compressed directly into tablets without any intermediate granulation of the powder before compression, as would normally be carried out. This has the advantage of being a simpler and cheaper method of production.

The invention thus also relates to an orally administered, solid pharmaceutical form of meloxicam from which the active substance is rapidly released and absorbed, for the treatment of pain, particularly for treating acute rheumatic attacks and for relieving acute pain, characterised in that meloxicam is present in the form of a salt with an inorganic or organic base, optionally together with conventional excipients and/or carriers, in a rapidly decomposing tablet produced by direct tabletting.

Suitable salts with an inorganic base include for example the sodium, potassium or ammonium salt of meloxicam. Examples of salts with organic bases include the meglumin salt, the Tris salt or a salt of meloxicam with a basic amino acid such as L-lysine or L-arginine. Salts which have proved particularly advantageous for the purposes of the present invention are the meglumin and sodium salt of meloxicam, the meloxicam-meglumin salt being particularly preferred, e.g. the meloxicam-meglumin salt dihydrate or more particularly the meloxicam-meglumin salt monohydrate.

Examples of excipients or carriers include microcrystalline cellulose, lactose, crosslinked polyvinylpyrrolidone, magnesium stearate, dicalcium phosphate and various starches.

Thirdly, the invention relates to a process for preparing an orally administered solid pharmaceutical preparation of meloxicam, which has a short decomposition time and from which the active substance is released and absorbed rapidly, for pain therapy, particularly for treating acute rheumatic attacks and for relieving acute pain, characterised in that an optionally pulverised meloxicam salt of an inorganic or organic base is intimately mixed with suitable pulverised excipients and/or carriers and compressed directly into tablets with no granulation of the powder before the compressing. The abovementioned meloxicam salts might be used, for example, the meglumin and the sodium salt of meloxicam being preferred. The meloxicam-meglumin salt is particularly preferred, for example the meloxicam-meglumin salt dihydrate or more particularly the meloxicam-meglumin salt monohydrate.

As already mentioned hereinbefore, the polymorphism and hygroscopy of the meloxicam-meglumin salt particularly led one to expect considerable difficulties in using the active substance in this form to achieve the objective of the invention, since only a reproducibly manufactured, uniform and stable modification can be used in a pharmaceutical formulation. Surprisingly, this condition can be met with the meloxicam-meglumin salt if, during crystallisation of the salt from a mixture of a water-miscible organic solvent and water, seed crystals consisting of crystalline meloxicam-meglumin salt monohydrate, preferably seed crystals of a meloxicam-meglumin salt monohydrate form previously crystallised from acetone/water, are added to the mixture. A product is then obtained, reproducibly and uniformly, which corresponds to the crystalline form of the seed crystals used.

From the crystalline meloxicam-meglumin salt monohydrate thus obtained, the crystalline meloxicam-meglumin salt dihydrate can be obtained by treating the monohydrate at high humidity.

As a result of the slight tendency to spontaneous crystallisation and the strong tendency to form different polymorphic forms it is advisable to seed the solution with crystals of the desired monohydrate form in the last step of the production of the solid meloxicam-meglumin salt for pharmaceutical use. If desired, the dihydrate form can then be obtained from the monohydrate form as mentioned above. The synthesis plan is shown in FIG. **2**.

Fourthly, the invention thus relates to the crystalline meloxicam-meglumin salt monohydrate, a process for preparing it, wherein meloxicam and meglumin are heated in a mixture of a water-miscible organic solvent and water and meloxicam-meglumin salt monohydrate seed crystals are added to the mixture for crystallisation, and an orally administered, solid pharmaceutical preparation containing meloxicam in the form of the crystalline meloxicam-meglumin salt monohydrate.

Examples of organic solvents include acetone, methanol, ethanol, n-propanol, i-propanol, tetrahydrofuran or dioxane, preferably acetone, ethanol, tetrahydrofuran and dioxane. Acetone and ethanol are particularly preferred, especially acetone.

In the mixture, organic solvent and water may be used in a ratio by volume of 10:1 to 100:1, preferably in a ratio of 20:1 to 50:1 or most preferably in a ratio of 35:1 to 45:1, a ratio of about 40:1 being particularly suitable when acetone is used.

Meloxicam and meglumin may for example be used in a molar ratio of 1:1.5 to 1.5:1, preferably in a molar ratio of 1:1.2 to 1.2:1, but particularly in an equimolar ratio.

Appropriately, the mixture may be heated with the addition of activated charcoal which is removed again before the addition of the seed crystals.

The amount of seed crystals added depends on the solvent system used and the quantity of mixture. For example, to a batch A=12.5 kg meloxicam, mixture B=5 to 50 g of meloxicam-meglumin salt monohydrate seed crystals (ratio by weight of A:B=125:0.05–0.5) are added, whilst if the solvent acetone/water is used the amount added is from 5 to 30 g, but particularly with a ratio of acetone: water=40:1 it is particularly appropriate to add 10 to 15 g of seed crystals. It is readily possible for the skilled man to determine the proper quantity of seed crystals for a given batch size and a given solvent system.

After the addition of the seed crystals the mixture is cooled to 10 to 30° C., but preferably to a temperature of about 20° C. Preferably, the mixture is then refluxed again and then slowly cooled to a temperature 10 and 30° C., preferably 15 to 25° C., but most usefully about 20° C. A fine crystalline crystal suspension of the desired meloxicam-meglumin salt monohydrate is obtained which is worked up in the usual way. The powder X-ray reflexes of the particularly preferred meloxicam meglumin salt monohydrate modification are contained in Table 2 which follows.

A fifth object of the invention is crystalline meloxicam-meglumin salt dihydrate, a process for preparing it, in which crystalline meloxicam-meglumin salt monohydrate is treated at high humidity, and an orally administered, solid pharmaceutical form containing meloxicam in the form of the crystalline meloxicam-meglumin salt dihydrate.

The treatment is carried out by storage for at least one day, preferably at least five days, at a high relative humidity. The relative humidity should be at least 75%, preferably at least 85%. The powder X-ray reflexes of the particularly preferred meloxicam meglumin salt dihydrate modification are shown in Table 3 which follows.

A sixth object of the invention is a process for preparing an orally administered solid pharmaceutical preparation containing meloxicam in the form of the meloxicam-meglumin salt monohydrate, which has a short decomposition time and from which the active substance is rapidly released and absorbed, for pain therapy, particularly for treating acute rheumatic attacks and for relieving acute pain, in which meloxicam and meglumin are heated in a mixture of a water-miscible organic solvent and water, meloxicam-meglumin salt monohydrate seed crystals are added to the mixture for crystallisation, then crystalline meloxicam-meglumin salt monohydrate is isolated in the usual way and powdered if desired and subsequently the meloxicam-meglumin salt monohydrate is intimately mixed with suitable powdered excipients and/or carriers and compressed directly into tablets with no granulation of the powder.

A seventh object of the invention is a process for preparing an orally administered solid pharmaceutical preparation containing meloxicam in the form of the meloxicam-meglumin salt dihydrate, which has a short decomposition time and from which the active substance is rapidly released and absorbed, for pain therapy, particularly for treating acute rheumatic attacks and for relieving acute pain, in which crystalline meloxicam-meglumin salt monohydrate is treated at high relative humidity, the meloxicam-meglumin salt dihydrate thus obtained is powdered, if desired, and then intimately mixed with suitable powdered excipients and/or carriers and compressed directly into tablets without granulation of the powder.

The following Examples are intended to illustrate the invention more fully:

EXAMPLE 1

Meloxicam Meglumin Salt Monohydrate

12.5 kg (35.57 mol) meloxicam and 6.9 kg (35.57 mol) meglumin are added successively, with stirring, to a mixture of 275 1 of acetone and 7:1 of water in a suitable reactor 1, then 1 kg of industrial-grade activated charcoal are added. The reaction mixture is heated and refluxed for 30 minutes. Then the mixture is forced through a pressure filter into a second reactor II. Reactor I and the pressure filter are washed out with 101 of acetone. The mixture is combined with 10–15 g meloxicam meglumin salt monohydrate seed crystals, cooled to 20° C. and stirred for 2 hours at this temperature. Then the mixture is heated, refluxed for 15 minutes and then slowly cooled to 20° C., during which time a fine crystalline crystal suspension is formed. This is stirred for 15 hours at 20° C. The crystal suspension is then centrifuged and subsequently spun dry. The centrifugal pellet is washed with 351 of acetone and again spun dry. The product is dried in the drying cupboard at 20–35° C. with fresh air for about 24 hours. Yield: 90.1% of theory; pale yellow crystalline powder, needle-like crystals; melting point: 120° C.

The crystalline meloxicam meglumin salt monohydrate thus obtained was investigated by IR-spectroscopy, by X-Ray Powder Diffraction and by thermal analysis (Thermogravimetry=TG; Differential Scanning Calorimetry=DSC).

1.1 IR Spectroscopy

Apparatus: Nicolet FTIR Spectrometer Magna—IR 550

Software: Nicolet Software Packet OMNIC, Version 1.20

Technique: Transmittance, KBr pellets (2.5 μmol substance/300 mg KBr), N2 rinse (flow: 151 N2/min)

The FTIR spectrum is shown in FIG. **5**. Compared with the FTIR spectrum of the dihydrate form there is a significant difference in the cleaved band at about 1300 cm^{-1} in the spectrum of the monohydrate form, otherwise the spectra are very similar.

1.2 X-ray Powder Diffraction

Apparatus: Philips X-Ray Powder Diffractometer, CuK_{α} radiation, α=1.5418 Å, 35 mA, 35 kV

Software: Software package GUFI 4.06 for data interpretation, Software package ORIGIN for data presentation

Parameters: Range: 3–50° 2Θ Step scan: 0.01° 2Θ step width, 2 sec counting time for each step

Appendix 12

TABLE 2

Powder X-Ray Reflexes and their intensities (standardised), meloxicam meglumin salt monohydrate

$2\Theta_{exp}$ [°]	d_{exp} [Å]	Intensity I/I_o
6.50	13.6	32
11.26	7.85	9
13.03	6.79	78
13.42	6.59	61
14.92	5.93	90
15.91	5.57	10
16.66	5.32	7
17.84	4.97	20
18.38	4.82	20
18.58	4.77	47
19.24	4.61	25
20.29	4.37	5
20.47	4.34	16
21.97	4.04	13
22.72	3.91	3
23.18	3.84	7
23.34	3.81	4
23.49	3.78	4
23.79	3.74	8
23.97	3.71	6
25.45	3.50	13
25.83	3.45	100
26.30	3.39	14
26.95	3.31	6
27.25	3.27	4
27.89	3.20	3
28.55	3.12	3
29.09	3.07	7
29.53	3.02	10
30.18	2.96	8
31.19	2.87	4
36.01	2.49	9
36.16	2.48	8
37.73	2.38	8
38.64	2.33	6
39.78	2.26	8

The X-ray powder diffraction pattern is shown in FIG. **6**.

1.3 Thermal Analysis

TG: Apparatus' Mettler Microbalance M3, Temperature-controller TC15

Software: Mettler Software package STAR

Technique: (—Al_2O_3 melting pot, heating rate: 10 K/min, N2 atmosphere

DSC: Apparatus: Mettler DSC-20, temperature controller TC15

Software: Mettler Software package STAR

Technique: open Al melting pot, heating rate: 3 and 10 K/min, N2 atmosphere

A clear correlation can be found between the endothermic peak observed in the DSC diagram and the dehydration or melting processes. Dehydration and melting are clearly separate processes.

The DSC diagram is shown in FIG. **8**.

EXAMPLE 2

Meloxicam Meglumin Salt Dihydrate

Crystalline meloxicam meglumin salt dihydrate is obtained by storing the crystalline meloxicam meglumin salt monohydrate obtained in Example 1 for five days over saturated potassium chloride solution at a relative humidity of 86% and a temperature of 20° C.

The crystalline meloxicam meglumin salt dihydrate thus obtained was investigated by IR-spectroscopy, by X-Ray Powder Diffraction and by thermal analysis (thermogravimetry=TG; Differential Scanning Calorimetry=DSC). The apparatus, software and parameters mentioned in Example 1 were used.

2.1 IR Spectroscopy: The FTIR Spectrum is Shown in FIG. **5**.

2.2 X-Ray Powder Diffraction:

TABLE 3

Powder X-Ray Reflexes and their intensities (standardised), meloxicam meglumin salt dihydrate

$2\Theta_{exp}$ [°]	d_{exp} [Å]	Intensity I/I_o
5.99	14.8	13
6.95	12.7	13
7.36	12.0	41
7.82	11.3	22
8.25	10.7	18
8.47	10.4	38
10.32	8.6	32
10.85	8.2	18
11.86	7.46	29
12.61	7.01	26
13.46	6.58	49
13.81	6.41	19
14.29	6.20	37
14.48	6.11	42
14.97	5.92	53
15.28	5.80	96
16.88	5.25	65
17.39	5.10	39
17.78	4.99	42
18.41	4.81	25
19.08	4.65	50
19.55	4.54	14
20.10	4.41	28
21.12	4.20	24
21.70	4.09	19
21.95	4.05	25
22.80	3.90	26
25.65	3.47	100
26.02	3.42	43
27.04	3.30	35
27.37	3.26	26
28.29	3.15	19
28.92	3.09	14
30.43	2.94	13

The X-ray powder diffraction pattern is shown in FIG. **6**.

2.3 Thermal Analysis

Clear correlation of the endothermic peak observed in the DSC diagram is not possible since dehydration and melting processes overlap.

The TG/DSC diagrams obtained are shown in FIGS. **8** and **9**.

The DSC diagram of the dihydrate form is very characteristic with a broad and structured endothermic peak between ambient temperature and 130° C. Five clear minima are visible at about 45, 65, 85, 115 and 125° C. The comparison with the DSC diagram of the monohydrate form in FIG. **8** clearly shows the differences between these two hydrate forms. All they have in common s the endothermic peaks at about 85–90° C. (dehydration step) and at about 125° C. (melting process).

EXAMPLE 3

Anhydrous Meloxicam Meglumin Salt

Meloxicam meglumin salt monohydrate can be converted into an anhydrous form by dehydration. The relevant parameters of the dehydration process are the temperature and duration of dehydration, the influence of which were observed by X-ray powder diffraction. The longer the dehydration process lasts, the less crystalline is the resulting

material. After 24 hours at 100° C. the meloxicam meglumin salt is anhydrous and totally amorphous, whereas after one hour at 80° C. no change can be detected in the monohydrate used. The X-ray powder diffraction diagrams obtained after 1 hour at 80° C., 15 hours at 70° C., 20 hours at 80° C. and 24 hours at 100° C. are shown in FIG. **7**.

EXAMPLE 4

Meloxicam Meglumin Salt (Monohydrate) Tablets, Directly Compressed

Recipe for meloxicam meglumin salt tablets:	
meloxicam meglumin salt calculated as meloxicam	7.5 mg
microcrystalline cellulose	205.5 mg
lactose	205.5 mg
polyvinylpyrrolidone (crosslinked)	22.5 mg
magnesium stearate	4.5 mg

Preparation:

The active substance (ground or not ground) is intimately mixed with the excipients specified in the recipe and compressed directly to form tablets.

EXAMPLE 5

Meloxicam Sodium Salt Tablets, Compressed Directly

Recipe for meloxicam sodium salt tablets:	
meloxicam sodium salt calculated as meloxicam	7.5 mg
microcrystalline cellulose	209.5 mg
lactose	205.5 mg
polyvinylpyrrolidone (crosslinked)	22.5 mg
magnesium stearate	4.5 mg

Preparation:

The active substance (ground or not ground) is prepared for example according to the data in EP-A-0 002 482, is intimately mixed with the excipients specified in the recipe and compressed directly to form tablets.

EXAMPLE 6

in Vitro Release:

Meloxicam (Neutral)/Directly Compressed Versus Meloxicam (Neutral)/Granulated/Compressed

When the release profiles of two tablets are compared with each other, one formulation having been produced by compressing a powder mixture whilst the other has been prepared by compressing previously granulated powder, it is apparent that the meloxicam is released more quickly from the tablet prepared by compressing of the powder mixture (FIG. **3**). The release was measured over the investigation period by spectral-photometric determination of the active substance at its extinction peak.

Recipe for meloxicam tablets: (directly compressed from powder)	
meloxicam	7.5 mg
microcrystalline cellulose	210.0 mg
lactose	205.0 mg
polyvinylpyrrolidone (crosslinked)	22.5 mg
magnesium stearate	4.5 mg

Recipe for meloxicam tablets: (compressed from granules)	
meloxicam	7.5 mg
microcrystalline cellulose	210.0 mg
lactose	205.0 mg
polyvinylpyrrolidone (crosslinked)	22.5 mg
magnesium stearate	4.5 mg

EXAMPLE 7

Human Trials for Verifying the Advantages of the Pharmaceutical Composition According to the Invention Over a Conventional Preparation

The following formulations were tested on 18 test subjects in a single dose in a cross-over trial:

Recipe for meloxicam meglumin salt tablets (directly compressed):	
meloxicam meglumin salt calculated as meloxicam	7.5 mg
microcrystalline cellulose	205.5 mg
lactose	205.5 mg
polyvinylpyrrolidone (crosslinked)	22.5 mg
magnesium stearate	4.5 mg

Recipe for meloxicam (granulated) capsules:	
meloxicam	7.5 mg
sodium citrate	15.0 mg
microcrystalline cellulose	102.0 mg
lactose	23.5 mg
polyvinylpyrrolidone (soluble)	10.5 mg
silicon dioxide (highly dispersed)	3.5 mg
polyvinylpyrrolidone (crosslinked)	16.3 mg
magnesium stearate	1.7 mg

FIG. **4** shows the averages of the plasma levels obtained. It is apparent that the differences found in the dissolution processes in vitro are also seen in the blood levels in humans after oral administration. When the rapidly released form with the salt of meloxicam was used, the plasma levels rose faster, leading to an increase in the maximum plasma levels and a shortening of the time taken to achieve these levels.

With an onset of activity correlated to the plasma level a formulation of this kind will give a faster acting analgesic effect.

What is claimed is:

1. Crystalline meloxicam meglumin salt monohydrate or crystalline meloxicam meglumin salt dihydrate.

2. A process for preparing crystalline meloxicam-meglumin salt monohydrate, the process comprising:

(a) heating meloxicam and meglumin in a solvent mixture of a water-miscible organic solvent and water; and

(b) adding meloxicam-meglumin salt monohydrate seed crystals to the solvent mixture containing meloxicam and meglumin to obtain crystalline meloxicam-meglumin salt monohydrate.

3. The process of claim **2**, wherein the water-miscible organic solvent is acetone, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, or dioxane.

4. The process of claim **2**, wherein the water-miscible organic solvent is acetone or ethanol.

5. The process of claim **2**, wherein the mixture of organic solvent and water are used in a ratio by volume of 10:1 to 100:1.

6. The process of claim **2**, wherein the meloxicam and meglumin are used in a molar ratio of 1:1.5 to 1.5:1.

7. The process of claim **2**, wherein a mixture of:

(A) 12.5 kg meloxicam; and

(B) 5 to 50 g of meloxicam-meglumin salt monohydrate seed crystals are added.

8. A process for preparing crystalline meloxicam-meglumin salt dihydrate, wherein crystalline meloxicam-meglumin salt monohydrate is treated at a relative humidity of at least 75%.

9. A process for preparing an orally administrable solid pharmaceutical preparation containing meloxicam in the form of the crystalline meloxicam-meglumin salt monohydrate, the process comprising:

(a) heating meloxicam and meglumin in a solvent mixture of a water-miscible organic solvent and water;

(b) adding meloxicam-meglumin salt monohydrate seed crystals to the solvent mixture containing meloxicam and meglumin to obtain crystalline meloxicam-meglumin salt monohydrate;

(c) separating crystalline meloxicam-meglumin salt monohydrate from the solvent mixture;

(d) optionally powdering the crystalline meloxicam-meglumin salt monohydrate and intimately mixing the crystalline meloxicam-meglumin salt monohydrate with a conventional powdered excipient or carrier to obtain a pharmaceutical mixture; and

(e) compressing the pharmaceutical mixture from step (d) directly into tablets with no granulation of the powder.

10. A process for preparing an orally administrable solid pharmaceutical preparation containing meloxicam in the form of the meloxicam-meglumin salt dihydrate, wherein crystalline meloxicam-meglumin salt monohydrate is treated at a relative humidity of at least 75%, the meloxicam-meglumin salt dihydrate thus obtained is optionally powdered, and then intimately mixed with suitable powdered excipient carrier and compressed directly into tablets without granulation of the powder.

11. A solid pharmaceutical composition for oral administration comprising meloxicam in the form of the crystalline meloxicam meglumin salt monohydrate.

12. A solid pharmaceutical composition for oral administration comprising meloxicam in the form of the crystalline meloxicam meglumin salt dihydrate.

13. The process of claim **2**, wherein a mixture of:

(A) meloxicam; and

(B) meloxicam-meglumin salt monohydrate seed crystals are added in a corresponding ratio by weight of A:B of 125:0.05–0.5.

14. The process of claim **2**, further comprising:

(c) separating crystalline meloxicam-meglumin salt monohydrate from the solvent mixture.

15. The composition in accordance with claim **11**, further comprising a conventional powered carrier or excipient.

16. The composition in accordance with claim **12**, further comprising a conventional powered carrier or excipient.

17. A method for the treatment of rheumatic diseases or acute pain, the method comprising orally administering a host suffering from rheumatic diseases or acute pain a therapeutic amount of composition in accordance with claim **11**.

18. A method for the treatment of rheumatic diseases or acute pain, the method comprising orally administering a host suffering rheumatic diseases or acute pain a therapeutic amount of composition in accordance with claim **12**.

* * * * *

Appendix 13

/ NDC (index.cfm)

National Drug Code Directory

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	43063-401-90	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	50268-526-15	15 mg/1	TABLET	ORAL	ANDA077918	AvPAK	50268-526	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-1630-4	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-1630	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	76420-039-07	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	42708-007-30	15 mg/1	TABLET	ORAL	ANDA077927	QPharma Inc	42708-007	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-14	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-30	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-60	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68071-3030-5	15 mg/1	TABLET	ORAL	ANDA077921	NuCare Pharmaceuticals,Inc.	68071-3030	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	61919-469-90	15 mg/1	TABLET	ORAL	ANDA077927	Direct Rx	61919-469	MELOXICAM	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	53002-2535-1	15 mg/1	TABLET	ORAL	ANDA077927	RPK Pharmaceuticals, Inc.	53002-2535	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	53002-2535-2	15 mg/1	TABLET	ORAL	ANDA077927	RPK Pharmaceuticals, Inc.	53002-2535	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	53002-2535-3	15 mg/1	TABLET	ORAL	ANDA077927	RPK Pharmaceuticals, Inc.	53002-2535	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	53002-2535-5	15 mg/1	TABLET	ORAL	ANDA077927	RPK Pharmaceuticals, Inc.	53002-2535	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	65862-098-05	15 mg/1	TABLET	ORAL	ANDA078008	Aurobindo Pharma Limited	65862-098	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	51655-571-26	15 mg/1	TABLET	ORAL	ANDA077929	Northwind Pharmaceuticals, LLC	51655-571	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	51655-571-52	15 mg/1	TABLET	ORAL	ANDA077929	Northwind Pharmaceuticals, LLC	51655-571	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	51655-571-84	15 mg/1	TABLET	ORAL	ANDA077929	Northwind Pharmaceuticals, LLC	51655-571	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	76282-153-30	15 mg/1	TABLET	ORAL	ANDA077927	Exelan Pharmaceuticals Inc.	76282-153	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-15	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	51407-611-10	15 mg/1	TABLET	ORAL	ANDA077918	Golden State Medical Supply, Inc.	51407-611	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	70518-1630-3	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-1630	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-0200-0	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-0200	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-0200-1	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-0200	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0083-1	15 mg/1	TABLET	ORAL	ANDA077929	Advanced Rx Pharmacy of Tennessee, LLC	80425-0083	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0083-2	15 mg/1	TABLET	ORAL	ANDA077929	Advanced Rx Pharmacy of Tennessee, LLC	80425-0083	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	70518-1828-1	15 mg/1	TABLET	ORAL	ANDA077921	REMEDYREPACK INC.	70518-1828	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	51655-577-26	15 mg/1	TABLET	ORAL	ANDA077927	Northwind Pharmaceuticals, LLC	51655-577	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	51655-577-52	15 mg/1	TABLET	ORAL	ANDA077927	Northwind Pharmaceuticals, LLC	51655-577	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	51655-577-84	15 mg/1	TABLET	ORAL	ANDA077927	Northwind Pharmaceuticals, LLC	51655-577	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	65841-051-01	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Lifesciences Limited	65841-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	65841-051-40	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Lifesciences Limited	65841-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	60760-419-07	15 mg/1	TABLET	ORAL	ANDA077927	St. Mary's Medical Park Pharmacy	60760-419	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	60760-419-60	15 mg/1	TABLET	ORAL	ANDA077927	St. Mary's Medical Park Pharmacy	60760-419	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	0615-8124-39	15 mg/1	TABLET	ORAL	ANDA077929	NCS HealthCare of KY, LLC dba Vangard Labs	0615-8124	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-0	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-1	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-2	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-3	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	71335-1888-4	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-5	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-6	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-7	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-8	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71335-1888-9	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	71335-1888	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	70518-1828-6	15 mg/1	TABLET	ORAL	ANDA077921	REMEDYREPACK INC.	70518-1828	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	51407-611-90	15 mg/1	TABLET	ORAL	ANDA077918	Golden State Medical Supply, Inc.	51407-611	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	70518-1828-4	15 mg/1	TABLET	ORAL	ANDA077921	REMEDYREPACK INC.	70518-1828	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	70518-1828-5	15 mg/1	TABLET	ORAL	ANDA077921	REMEDYREPACK INC.	70518-1828	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	65841-051-77	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Lifesciences Limited	65841-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-0200-3	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-0200	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-00	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-07	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	43063-401-14	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	43063-401-28	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-1630-2	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-1630	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43353-979-30	15 mg/1	TABLET	ORAL	ANDA077918	Aphena Pharma Solutions - Tennessee, LLC	43353-979	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	71205-924-11	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-14	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-15	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	76282-153-05	15 mg/1	TABLET	ORAL	ANDA077927	Exelan Pharmaceuticals Inc.	76282-153	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-28	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-0	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-1	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-2	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-20	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	60760-653-07	15 mg/1	TABLET	ORAL	ANDA077929	ST. MARY'S MEDICAL PARK PHARMACY	60760-653	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	60760-653-30	15 mg/1	TABLET	ORAL	ANDA077929	ST. MARY'S MEDICAL PARK PHARMACY	60760-653	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	60760-653-60	15 mg/1	TABLET	ORAL	ANDA077929	ST. MARY'S MEDICAL PARK PHARMACY	60760-653	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71610-580-30	15 mg/1	TABLET	ORAL	ANDA077921	Aphena Pharma Solutions - Tennessee, LLC	71610-580	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71610-580-60	15 mg/1	TABLET	ORAL	ANDA077921	Aphena Pharma Solutions - Tennessee, LLC	71610-580	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	70934-011-30	15 mg/1	TABLET	ORAL	ANDA077927	Denton Pharma, Inc. DBA Northwind Pharmaceuticals	70934-011	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	70934-011-90	15 mg/1	TABLET	ORAL	ANDA077927	Denton Pharma, Inc. DBA Northwind Pharmaceuticals	70934-011	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	43063-401-30	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	76282-153-01	15 mg/1	TABLET	ORAL	ANDA077927	Exelan Pharmaceuticals Inc.	76282-153	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	76282-153-10	15 mg/1	TABLET	ORAL	ANDA077927	Exelan Pharmaceuticals Inc.	76282-153	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	72865-138-01	15 mg/1	TABLET	ORAL	ANDA077927	XLCare Pharmaceuticals, Inc.	72865-138	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	72865-138-10	15 mg/1	TABLET	ORAL	ANDA077927	XLCare Pharmaceuticals, Inc.	72865-138	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	72865-138-90	15 mg/1	TABLET	ORAL	ANDA077927	XLCare Pharmaceuticals, Inc.	72865-138	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-30	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-55	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-60	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-72	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71205-924-90	15 mg/1	TABLET	ORAL	ANDA077918	Proficient Rx LP	71205-924	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	43602-624-10	15 mg/1	TABLET	ORAL	ANDA217579	Ascent Pharmaceuticals, Inc	43602-624	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	43602-624-30	15 mg/1	TABLET	ORAL	ANDA217579	Ascent Pharmaceuticals, Inc	43602-624	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	61919-469-60	15 mg/1	TABLET	ORAL	ANDA077927	Direct Rx	61919-469	MELOXICAM	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	70518-1828-2	15 mg/1	TABLET	ORAL	ANDA077921	REMEDYREPACK INC.	70518-1828	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68382-051-01	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Pharmaceuticals USA Inc.	68382-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0044-1	15 mg/1	TABLET	ORAL	ANDA077927	Advanced Rx Pharmacy of Tennessee, LLC	80425-0044	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0044-2	15 mg/1	TABLET	ORAL	ANDA077927	Advanced Rx Pharmacy of Tennessee, LLC	80425-0044	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0045-1	15 mg/1	TABLET	ORAL	ANDA077921	Advanced Rx Pharmacy of Tennessee, LLC	80425-0045	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43063-396-15	15 mg/1	TABLET	ORAL	ANDA077918	PD-Rx Pharmaceuticals, Inc.	43063-396	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	60760-419-30	15 mg/1	TABLET	ORAL	ANDA077927	St. Mary's Medical Park Pharmacy	60760-419	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-0	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-1	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-2	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-3	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-4	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-6	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5339-7	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5339	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71610-657-30	15 mg/1	TABLET	ORAL	ANDA077918	Aphena Pharma Solutions - Tennessee, LLC	71610-657	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	71610-657-60	15 mg/1	TABLET	ORAL	ANDA077918	Aphena Pharma Solutions - Tennessee, LLC	71610-657	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	76420-039-14	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	76420-039-20	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	67296-1460-3	15 mg/1	TABLET	ORAL	ANDA077921	Redpharm Drug, Inc.	67296-1460	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-0	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-1	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-2	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-3	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-4	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	71335-2327-5	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-6	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-7	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-8	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	71335-2327-9	15 mg/1	TABLET	ORAL	ANDA077929	Bryant Ranch Prepack	71335-2327	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	29300-125-19	15 mg/1	TABLET	ORAL	ANDA077927	Unichem Pharmaceuticals (USA), Inc.	29300-125	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	68071-2184-3	15 mg/1	TABLET	ORAL	ANDA077929	NuCare Pharmaceuticals, Inc.	68071-2184	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	68071-2184-9	15 mg/1	TABLET	ORAL	ANDA077929	NuCare Pharmaceuticals, Inc.	68071-2184	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6671-0	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	50090-6671-1	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6671-2	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6671-3	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6671-4	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6671-6	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6671-7	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6671	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	50090-6672-0	15 mg/1	TABLET	ORAL	ANDA077929	A-S Medication Solutions	50090-6672	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-0	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-1	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	63629-3328-2	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-3	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-4	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-5	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-6	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-7	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-8	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63629-3328-9	15 mg/1	TABLET	ORAL	ANDA077927	Bryant Ranch Prepack	63629-3328	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	82009-130-05	15 mg/1	TABLET	ORAL	ANDA077921	Quallent Pharmaceuticals Health LLC	82009-130	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	71610-544-53	15 mg/1	TABLET	ORAL	ANDA077927	Aphena Pharma Solutions - Tennessee, LLC	71610-544	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	63629-2019-1	15 mg/1	TABLET	ORAL	ANDA077918	Bryant Ranch Prepack	63629-2019	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	67296-0823-1	15 mg/1	TABLET	ORAL	ANDA077927	RedPharm Drug, Inc.	67296-0823	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	67296-0823-5	15 mg/1	TABLET	ORAL	ANDA077927	RedPharm Drug, Inc.	67296-0823	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	67296-0823-7	15 mg/1	TABLET	ORAL	ANDA077927	RedPharm Drug, Inc.	67296-0823	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	49999-869-30	15 mg/1	TABLET	ORAL	ANDA077927	Quality Care Products LLC	49999-869	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	49999-869-90	15 mg/1	TABLET	ORAL	ANDA077927	Quality Care Products LLC	49999-869	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	65841-051-05	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Lifesciences Limited	65841-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	65841-051-16	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Lifesciences Limited	65841-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	69097-159-12	15 mg/1	TABLET	ORAL	ANDA077929	Cipla USA Inc.	69097-159	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	69097-159-15	15 mg/1	TABLET	ORAL	ANDA077929	Cipla USA Inc.	69097-159	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	61442-127-10	15 mg/1	TABLET	ORAL	ANDA077918	Carlsbad Technology, Inc.	61442-127	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68382-051-77	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Pharmaceuticals USA Inc.	68382-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-10	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68071-3030-7	15 mg/1	TABLET	ORAL	ANDA077921	NuCare Pharmaceuticals,Inc.	68071-3030	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68071-3030-9	15 mg/1	TABLET	ORAL	ANDA077921	NuCare Pharmaceuticals,Inc.	68071-3030	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43063-396-07	15 mg/1	TABLET	ORAL	ANDA077918	PD-Rx Pharmaceuticals, Inc.	43063-396	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	43063-401-15	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	71335-1956-3	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-4	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-5	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0044-3	15 mg/1	TABLET	ORAL	ANDA077927	Advanced Rx Pharmacy of Tennessee, LLC	80425-0044	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-6	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-7	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-8	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	43063-401-06	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	76420-039-10	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	76420-039-30	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	76420-039-60	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	76420-039-90	15 mg/1	TABLET	ORAL	ANDA077927	Asclemed USA, Inc.	76420-039	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	64380-716-06	15 mg/1	TABLET	ORAL	ANDA077928	Strides Pharma Science Limited	64380-716	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43063-396-30	15 mg/1	TABLET	ORAL	ANDA077918	PD-Rx Pharmaceuticals, Inc.	43063-396	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43063-396-90	15 mg/1	TABLET	ORAL	ANDA077918	PD-Rx Pharmaceuticals, Inc.	43063-396	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	16571-777-01	15 mg/1	TABLET	ORAL	ANDA078008	Rising Pharma Holdings, Inc.	16571-777	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	16571-777-10	15 mg/1	TABLET	ORAL	ANDA078008	Rising Pharma Holdings, Inc.	16571-777	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	16571-777-50	15 mg/1	TABLET	ORAL	ANDA078008	Rising Pharma Holdings, Inc.	16571-777	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	31722-227-01	15 mg/1	TABLET	ORAL	ANDA217579	Camber Pharmaceuticals, Inc.	31722-227	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	31722-227-05	15 mg/1	TABLET	ORAL	ANDA217579	Camber Pharmaceuticals, Inc.	31722-227	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	31722-227-31	15 mg/1	TABLET	ORAL	ANDA217579	Camber Pharmaceuticals, Inc.	31722-227	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	29300-125-01	15 mg/1	TABLET	ORAL	ANDA077927	Unichem Pharmaceuticals (USA), Inc.	29300-125	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	29300-125-10	15 mg/1	TABLET	ORAL	ANDA077927	Unichem Pharmaceuticals (USA), Inc.	29300-125	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	29300-125-13	15 mg/1	TABLET	ORAL	ANDA077927	Unichem Pharmaceuticals (USA), Inc.	29300-125	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	29300-125-50	15 mg/1	TABLET	ORAL	ANDA077927	Unichem Pharmaceuticals (USA), Inc.	29300-125	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68382-051-16	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Pharmaceuticals USA Inc.	68382-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68382-051-40	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Pharmaceuticals USA Inc.	68382-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	43353-979-60	15 mg/1	TABLET	ORAL	ANDA077918	Aphena Pharma Solutions - Tennessee, LLC	43353-979	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	68462-141-01	15 mg/1	TABLET	ORAL	ANDA077932	Glenmark Pharmaceuticals Inc., USA	68462-141	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	50090-5340-0	15 mg/1	TABLET	ORAL	ANDA077921	A-S Medication Solutions	50090-5340	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	60687-199-01	15 mg/1	TABLET	ORAL	ANDA077921	American Health Packaging	60687-199	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68788-7904-1	15 mg/1	TABLET	ORAL	ANDA077921	Preferred Pharmaceuticals Inc.	68788-7904	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68788-7904-3	15 mg/1	TABLET	ORAL	ANDA077921	Preferred Pharmaceuticals Inc.	68788-7904	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68788-7904-6	15 mg/1	TABLET	ORAL	ANDA077921	Preferred Pharmaceuticals Inc.	68788-7904	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	68788-7904-9	15 mg/1	TABLET	ORAL	ANDA077921	Preferred Pharmaceuticals Inc.	68788-7904	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	80425-0045-2	15 mg/1	TABLET	ORAL	ANDA077921	Advanced Rx Pharmacy of Tennessee, LLC	80425-0045	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ MELOXICAM	61919-469-07	15 mg/1	TABLET	ORAL	ANDA077927	Direct Rx	61919-469	MELOXICAM	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	61919-469-15	15 mg/1	TABLET	ORAL	ANDA077927	Direct Rx	61919-469	MELOXICAM	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-1630-5	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-1630	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	60760-653-90	15 mg/1	TABLET	ORAL	ANDA077929	ST. MARY'S MEDICAL PARK PHARMACY	60760-653	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	11788-047-01	15 mg/1	TABLET	ORAL	ANDA217579	AiPing Pharmaceutical, Inc	11788-047	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	11788-047-03	15 mg/1	TABLET	ORAL	ANDA217579	AiPing Pharmaceutical, Inc	11788-047	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	11788-047-05	15 mg/1	TABLET	ORAL	ANDA217579	AiPing Pharmaceutical, Inc	11788-047	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	11788-047-10	15 mg/1	TABLET	ORAL	ANDA217579	AiPing Pharmaceutical, Inc	11788-047	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43063-396-60	15 mg/1	TABLET	ORAL	ANDA077918	PD-Rx Pharmaceuticals, Inc.	43063-396	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	80425-0083-3	15 mg/1	TABLET	ORAL	ANDA077929	Advanced Rx Pharmacy of Tennessee, LLC	80425-0083	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-07	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-10	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-14	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-15	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-28	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-30	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-60	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	82804-029-90	15 mg/1	TABLET	ORAL	ANDA077929	Proficient Rx LP	82804-029	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	62135-716-18	15 mg/1	TABLET	ORAL	ANDA077920	Chartwell RX, LLC	62135-716	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	62135-716-90	15 mg/1	TABLET	ORAL	ANDA077920	Chartwell RX, LLC	62135-716	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71610-542-30	15 mg/1	TABLET	ORAL	ANDA077918	Aphena Pharma Solutions - Tennessee, LLC	71610-542	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71610-542-60	15 mg/1	TABLET	ORAL	ANDA077918	Aphena Pharma Solutions - Tennessee, LLC	71610-542	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71610-544-30	15 mg/1	TABLET	ORAL	ANDA077927	Aphena Pharma Solutions - Tennessee, LLC	71610-544	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	71610-544-60	15 mg/1	TABLET	ORAL	ANDA077927	Aphena Pharma Solutions - Tennessee, LLC	71610-544	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-1630-0	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-1630	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-1630-6	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-1630	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-0200-4	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-0200	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ Meloxicam	64380-716-07	15 mg/1	TABLET	ORAL	ANDA077928	Strides Pharma Science Limited	64380-716	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	63187-083-90	15 mg/1	TABLET	ORAL	ANDA077927	Proficient Rx LP	63187-083	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-0171-0	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-0171	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	65862-098-99	15 mg/1	TABLET	ORAL	ANDA078008	Aurobindo Pharma Limited	65862-098	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	60760-419-90	15 mg/1	TABLET	ORAL	ANDA077927	St. Mary's Medical Park Pharmacy	60760-419	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	61919-469-30	15 mg/1	TABLET	ORAL	ANDA077927	Direct Rx	61919-469	MELOXICAM	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	69097-159-07	15 mg/1	TABLET	ORAL	ANDA077929	Cipla USA Inc.	69097-159	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	65862-098-01	15 mg/1	TABLET	ORAL	ANDA078008	Aurobindo Pharma Limited	65862-098	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ MELOXICAM	70518-0200-2	15 mg/1	TABLET	ORAL	ANDA077929	REMEDYREPACK INC.	70518-0200	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name
+ meloxicam	68382-051-05	15 mg/1	TABLET	ORAL	ANDA077921	Zydus Pharmaceuticals USA Inc.	68382-051	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	49999-869-15	15 mg/1	TABLET	ORAL	ANDA077927	Quality Care Products LLC	49999-869	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	49999-869-60	15 mg/1	TABLET	ORAL	ANDA077927	Quality Care Products LLC	49999-869	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	43063-401-60	15 mg/1	TABLET	ORAL	ANDA077927	PD-Rx Pharmaceuticals, Inc.	43063-401	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ Meloxicam	43063-396-95	15 mg/1	TABLET	ORAL	ANDA077918	PD-Rx Pharmaceuticals, Inc.	43063-396	Meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG
+ meloxicam	71335-1956-9	15 mg/1	TABLET	ORAL	ANDA077921	Bryant Ranch Prepack	71335-1956	meloxicam	MELOXICAM	HUMAN PRESCRIPTION DRUG

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Background Information (https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)

Drug questions email: **DRUGINFO@FDA.HHS.GOV (mailto:DRUGINFO@FDA.HHS.Gov)**

See also: **Drug Registration and Listing Instructions (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm)**
National Drug Code Directory Data Files (https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)

U.S Department of Health and Human Services

Appendix 13

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services

Public Law 103-396
103d Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to clarify the application of the Act with respect to alternate uses of new animal drugs and new drugs intended for human use, and for other purposes.

Oct. 22, 1994
[S. 340]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Animal Medicinal Drug Use Clarification Act of 1994.
21 USC 301 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Animal Medicinal Drug Use Clarification Act of 1994".

SEC. 2. UNAPPROVED USES.

(a) GENERAL RULE.—Section 512(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(a)) is amended by adding the following new paragraphs at the end:

"(4)(A) Except as provided in subparagraph (B), if an approval of an application filed under subsection (b) is in effect with respect to a particular use or intended use of a new animal drug, the drug shall not be deemed unsafe for the purposes of paragraph (1) and shall be exempt from the requirements of section 502(f) with respect to a different use or intended use of the drug, other than a use in or on animal feed, if such use or intended use—

"(i) is by or on the lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship, as defined by the Secretary; and

"(ii) is in compliance with regulations promulgated by the Secretary that establish the conditions for such different use or intended use.

The regulations promulgated by the Secretary under clause (ii) may prohibit particular uses of an animal drug and shall not permit such different use of an animal drug if the labeling of another animal drug that contains the same active ingredient and which is in the same dosage form and concentration provides for such different use.

"(B) If the Secretary finds that there is a reasonable probability that a use of an animal drug authorized under subparagraph (A) may present a risk to the public health, the Secretary may—

"(i) establish a safe level for a residue of an animal drug when it is used for such different use authorized by subparagraph (A); and

"(ii) require the development of a practical, analytical method for the detection of residues of such drug above the safe level established under clause (i).

The use of an animal drug that results in residues exceeding a safe level established under clause (i) shall be considered an unsafe use of such drug under paragraph (1). Safe levels may be established under clause (i) either by regulation or order.

"(C) The Secretary may by general regulation provide access to the records of veterinarians to ascertain any use or intended use authorized under subparagraph (A) that the Secretary has determined may present a risk to the public health.

"(D) If the Secretary finds, after affording an opportunity for public comment, that a use of an animal drug authorized under subparagraph (A) presents a risk to the public health or that an analytical method required under subparagraph (B) has not been developed and submitted to the Secretary, the Secretary may, by order, prohibit any such use.

"(5) If the approval of an application filed under section 505 is in effect, the drug under such application shall not be deemed unsafe for purposes of paragraph (1) and shall be exempt from the requirements of section 502(f) with respect to a use or intended use of the drug in animals if such use or intended use—

"(A) is by or on the lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship, as defined by the Secretary; and

"(B) is in compliance with regulations promulgated by the Secretary that establish the conditions for the use or intended use of the drug in animals.".

(b) OTHER AMENDMENTS.—

(1) SECTION 301.—Section 301 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331) is amended—

(A) in paragraph (e), by striking "507(d) or (g)," and inserting "507(d) or (g), 512(a)(4)(C),"; and

(B) by adding at the end the following:

"(u) The failure to comply with any requirements of the provisions of, or any regulations or orders of the Secretary, under section 512(a)(4)(A), 512(a)(4)(D), or 512(a)(5).".

(2) SECTION 512(e).—Section 512(e)(1)(A) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360b(e)(1)(A)) is amended by inserting before the semicolon the following: "or the condition of use authorized under subsection (a)(4)(A)".

(3) SECTION 512(l).—Section 512(l)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(l)(1)) is amended by striking "relating to experience" and inserting "relating to experience, including experience with uses authorized under subsection (a)(4)(A),".

21 USC 360b note.

(c) REGULATIONS.—Not later than 2 years after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate regulations to implement paragraphs (4)(A) and (5) of section 512(a) of the Federal Food, Drug, and Cosmetic Act (as amended by subsection (a)).

21 USC 360b note.

(d) EFFECTIVE DATE.—The amendments made by this section shall take effect upon the adoption of the final regulations under subsection (c).

SEC. 3. MAPLE SYRUP.

(a) PREEMPTION.—Section 403A(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343–1(a)) is amended—

(1) in paragraph (1), by inserting at the end the following: "except that this paragraph does not apply to a standard of

identity of a State or political subdivision of a State for maple syrup that is of the type required by sections 401 and 403(g),";

(2) in paragraph (2), by inserting at the end the following: "except that this paragraph does not apply to a requirement of a State or political subdivision of a State that is of the type required by section 403(c) and that is applicable to maple syrup,"; and

(3) in paragraph (3) by inserting at the end the following: "except that this paragraph does not apply to a requirement of a State or political subdivision of a State that is of the type required by section 403(h)(1) and that is applicable to maple syrup,".

(b) PROCEDURE.—Section 701(e)(1) (21 U.S.C. 371(e)(1)) is amended by striking "or maple syrup (regulated under section 168.140 of title 21, Code of Federal Regulations).".

Approved October 22, 1994.

LEGISLATIVE HISTORY—S. 340:

CONGRESSIONAL RECORD, Vol. 140 (1994):
Oct. 4, considered and passed Senate.
Oct. 6, considered and passed House.

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Displaying title 21, up to date as of 1/23/2024. Title 21 was last amended 1/22/2024.

Title 21 —Food and Drugs
Chapter I —Food and Drug Administration, Department of Health and Human Services
Subchapter E —Animal Drugs, Feeds, and Related Products

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PART 530—EXTRALABEL DRUG USE IN ANIMALS

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 360b, 371, 379e.

Source: 61 FR 57743, Nov. 7, 1996, unless otherwise noted.

Subpart A—General Provisions

§ 530.1 Scope.

This part applies to the extralabel use in an animal of any approved new animal drug or approved new human drug by or on the lawful order of a licensed veterinarian within the context of a valid veterinary-client-patient relationship.

§ 530.2 Purpose.

The purpose of this part is to establish conditions for extralabel use or intended extralabel use in animals by or on the lawful order of licensed veterinarians of Food and Drug Administration approved new animal drugs and approved new human drugs. Such use is limited to treatment modalities when the health of an animal is threatened or suffering or death may result from failure to treat. This section implements the Animal Medicinal Drug Use Clarification Act of 1994 (the AMDUCA) (Pub. L. 103–396).

§ 530.3 Definitions.

(a) ***Extralabel use*** means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.

(b) ***FDA*** means the U.S. Food and Drug Administration.

(c) The phrase *a reasonable probability that a drug's use may present a risk to the public health* means that FDA has reason to believe that use of a drug may be likely to cause a potential adverse event.

(d) The phrase *use of a drug may present a risk to the public health* means that FDA has information that indicates that use of a drug may cause an adverse event.

(e) The phrase *use of a drug presents a risk to the public health* means that FDA has evidence that demonstrates that the use of a drug has caused or likely will cause an adverse event.

(f) A *residue* means any compound present in edible tissues that results from the use of a drug, and includes the drug, its metabolites, and any other substance formed in or on food because of the drug's use.

(g) A *safe level* is a conservative estimate of a drug residue level in edible animal tissue derived from food safety data or other scientific information. Concentrations of residues in tissue below the safe level will not raise human food safety concerns. A safe level is not a safe concentration or a tolerance and does not indicate that an approval exists for the drug in that species or category of animal from which the food is derived.

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(h) ***Veterinarian*** means a person licensed by a State or Territory to practice veterinary medicine.

(i) A *valid veterinarian-client-patient relationship* is one in which:

(1) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian;

(2) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and

(3) The practicing veterinarian is readily available for followup in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.

§ 530.4 Advertising and promotion.

Nothing in this part shall be construed as permitting the advertising or promotion of extralabel uses in animals of approved new animal drugs or approved human drugs.

§ 530.5 Veterinary records.

(a) As a condition of extralabel use permitted under this part, to permit FDA to ascertain any extralabel use or intended extralabel use of drugs that the agency has determined may present a risk to the public health, veterinarians shall maintain the following records of extralabel uses. Such records shall be legible, documented in an accurate and timely manner, and be readily accessible to permit prompt retrieval of information. Such records shall be adequate to substantiate the identification of the animals and shall be maintained either as individual records or, in food animal practices, on a group, herd, flock, or per-client basis. Records shall be adequate to provide the following information:

(1) The established name of the drug and its active ingredient, or if formulated from more than one ingredient, the established name of each ingredient;

(2) The condition treated;

(3) The species of the treated animal(s);

(4) The dosage administered;

(5) The duration of treatment;

(6) The numbers of animals treated; and

(7) The specified withdrawal, withholding, or discard time(s), if applicable, for meat, milk, eggs, or any food which might be derived from any food animals treated.

(b) A veterinarian shall keep all required records for 2 years or as otherwise required by Federal or State law, whichever is greater.

(c) Any person who is in charge, control, or custody of such records shall, upon request of a person

designated by FDA, permit such person designated by FDA to, at all reasonable times, have access to, permit copying, and verify such records.

Subpart B—Rules and Provisions for Extralabel Uses of Drugs in Animals

§ 530.10 Provision permitting extralabel use of animal drugs.

An approved new animal drug or human drug intended to be used for an extralabel purpose in an animal is not unsafe under section 512 of the act and is exempt from the labeling requirements of section 502(f) of the act if such use is:

(a) By or on the lawful written or oral order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship; and

(b) In compliance with this part.

§ 530.11 Limitations.

In addition to uses which do not comply with the provision set forth in § 530.10, the following specific extralabel uses are not permitted and result in the drug being deemed unsafe within the meaning of section 512 of the act:

(a) Extralabel use in an animal of an approved new animal drug or human drug by a lay person (except when under the supervision of a licensed veterinarian);

(b) Extralabel use of an approved new animal drug or human drug in or on an animal feed;

(c) Extralabel use resulting in any residue which may present a risk to the public health; and

(d) Extralabel use resulting in any residue above an established safe level, safe concentration or tolerance.

§ 530.12 Labeling.

Any human or animal drug prescribed and dispensed for extralabel use by a veterinarian or dispensed by a pharmacist on the order of a veterinarian shall bear or be accompanied by labeling information adequate to assure the safe and proper use of the product. Such information shall include the following:

(a) The name and address of the prescribing veterinarian. If the drug is dispensed by a pharmacy on the order of a veterinarian, the labeling shall include the name of the prescribing veterinarian and the name and address of the dispensing pharmacy, and may include the address of the prescribing veterinarian;

(b) The established name of the drug or, if formulated from more than one active ingredient, the established name of each ingredient;

(c) Any directions for use specified by the veterinarian, including the class/species or identification of the animal or herd, flock, pen, lot, or other group of animals being treated, in which the drug is intended to be used; the dosage, frequency, and route of administration; and the duration of therapy;

(d) Any cautionary statements; and

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(e) The veterinarian's specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food which might be derived from the treated animal or animals.

§ 530.13 Extralabel use from compounding of approved new animal and approved human drugs.

(a) This part applies to compounding of a product from approved animal or human drugs by a veterinarian or a pharmacist on the order of a veterinarian within the practice of veterinary medicine. Nothing in this part shall be construed as permitting compounding from bulk drugs.

(b) Extralabel use from compounding of approved new animal or human drugs is permitted if:

(1) All relevant portions of this part have been complied with;

(2) There is no approved new animal or approved new human drug that, when used as labeled or in conformity with criteria established in this part, will, in the available dosage form and concentration, appropriately treat the condition diagnosed. Compounding from a human drug for use in food-producing animals will not be permitted if an approved animal drug can be used for the compounding;

(3) The compounding is performed by a licensed pharmacist or veterinarian within the scope of a professional practice;

(4) Adequate procedures and processes are followed that ensure the safety and effectiveness of the compounded product;

(5) The scale of the compounding operation is commensurate with the established need for compounded products (e.g., similar to that of comparable practices); and

(6) All relevant State laws relating to the compounding of drugs for use in animals are followed.

(c) Guidance on the subject of compounding may be found in guidance documents issued by FDA.

Subpart C—Specific Provisions Relating to Extralabel Use of Animal and Human Drugs in Food-Producing Animals

§ 530.20 Conditions for permitted extralabel animal and human drug use in food-producing animals.

(a) The following conditions must be met for a permitted extralabel use in food-producing animals of approved new animal and human drugs:

(1) There is no approved new animal drug that is labeled for such use and that contains the same active ingredient which is in the required dosage form and concentration, except where a veterinarian finds, within the context of a valid veterinarian-client-patient relationship, that the approved new animal drug is clinically ineffective for its intended use.

(2) Prior to prescribing or dispensing an approved new animal or human drug for an extralabel use in food animals, the veterinarian must:

(i) Make a careful diagnosis and evaluation of the conditions for which the drug is to be used;

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(ii) Establish a substantially extended withdrawal period prior to marketing of milk, meat, eggs, or other edible products supported by appropriate scientific information, if applicable;

(iii) Institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and

(iv) Take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extralabel treatment.

(b) The following additional conditions must be met for a permitted extralabel use of in food-producing animals an approved human drug, or of an animal drug approved only for use in animals not intended for human consumption:

(1) Such use must be accomplished in accordance with an appropriate medical rationale; and

(2) If scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply.

(c) Extralabel use of an approved human drug in a food-producing animal is not permitted under this part if an animal drug approved for use in food-producing animals can be used in an extralabel manner for the particular use.

§ 530.21 Prohibitions for food-producing animals.

(a) FDA may prohibit the extralabel use of an approved new animal or human drug or class of drugs in food-producing animals if FDA determines that:

(1) An acceptable analytical method needs to be established and such method has not been established or cannot be established; or

(2) The extralabel use of the drug or class of drugs presents a risk to the public health.

(b) A prohibition may be a general ban on the extralabel use of the drug or class of drugs or may be limited to a specific species, indication, dosage form, route of administration, or combination of factors.

§ 530.22 Safe levels and analytical methods for food-producing animals.

(a) FDA may establish a safe level for extralabel use of an approved human drug or an approved new animal drug when the agency finds that there is a reasonable probability that an extralabel use may present a risk to the public health. FDA may:

(1) Establish a finite safe level based on residue and metabolism information from available sources;

(2) Establish a safe level based on the lowest level that can be measured by a practical analytical method; or

(3) Establish a safe level based on other appropriate scientific, technical, or regulatory criteria.

(b) FDA may require the development of an acceptable analytical method for the quantification of

residues above any safe level established under this part. If FDA requires the development of such an acceptable analytical method, the agency will publish notice of that requirement in the FEDERAL REGISTER.

(c) The extralabel use of an animal drug or human drug that results in residues exceeding a safe level established under this part is an unsafe use of such drug.

(d) If the agency establishes a safe level for a particular species or category of animals and a tolerance or safe concentration is later established through an approval for that particular species or category of animals, for that species or category of animals, the safe level is superseded by the tolerance or safe concentration for that species or category of animals.

§ 530.23 Procedure for setting and announcing safe levels.

(a) FDA may issue an order establishing a safe level for a residue of an extralabel use of an approved human drug or an approved animal drug. The agency will publish in the FEDERAL REGISTER a notice of the order. The notice will include:

(1) A statement setting forth the agency's finding that there is a reasonable probability that extralabel use in animals of the human drug or animal drug may present a risk to the public health;

(2) A statement of the basis for that finding; and

(3) A request for public comments.

(b) A current listing of those drugs for which a safe level for extralabel drug use in food-producing animals has been established, the specific safe levels, and the availability, if any, of a specific analytical method or methods for drug residue detection will be codified in § 530.40.

§ 530.24 Procedure for announcing analytical methods for drug residue quantification.

(a) FDA may issue an order announcing a specific analytical method or methods for the quantification of extralabel use drug residues above the safe levels established under § 530.22 for extralabel use of an approved human drug or an approved animal drug. The agency will publish in the FEDERAL REGISTER a notice of the order, including the name of the specific analytical method or methods and the drug or drugs for which the method is applicable.

(b) Copies of analytical methods for the quantification of extralabel use drug residues above the safe levels established under § 530.22 will be available upon request from the Communications and Education Branch (HFV–12), Division of Program Communication and Administrative Management, Center for Veterinary Medicine, 7500 Standish Pl., Rockville, MD 20855. When an analytical method for the detection of extralabel use drug residues above the safe levels established under § 530.22 is developed, and that method is acceptable to the agency, FDA will incorporate that method by reference.

§ 530.25 Orders prohibiting extralabel uses for drugs in food-producing animals.

(a) FDA may issue an order prohibiting extralabel use of an approved new animal or human drug in food-producing animals if the agency finds, after providing an opportunity for public comment, that:

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(1) An acceptable analytical method required under § 530.22 has not been developed, submitted, and found to be acceptable by FDA or that such method cannot be established; or

(2) The extralabel use in animals presents a risk to the public health.

(b) After making a determination that the analytical method required under § 530.22 has not been developed and submitted, or that such method cannot be established, or that an extralabel use in animals of a particular human drug or animal drug presents a risk to the public health, FDA will publish in the FEDERAL REGISTER, with a 90-day delayed effective date, an order of prohibition for an extralabel use of a drug in food-producing animals. Such order shall state that an acceptable analytical method required under § 530.22 has not been developed, submitted, and found to be acceptable by FDA; that such method cannot be established; or that the extralabel use in animals presents a risk to the public health; and shall:

(1) Specify the nature and extent of the order of prohibition and the reasons for the prohibition;

(2) Request public comments; and

(3) Provide a period of not less than 60 days for comments.

(c) The order of prohibition will become effective 90 days after date of publication of the order unless FDA publishes a notice in the FEDERAL REGISTER prior to that date, that revokes the order of prohibition, modifies it, or extends the period of public comment.

(d) The agency may publish an order of prohibition with a shorter comment period and/or delayed effective date than specified in paragraph (b) of this section in exceptional circumstances (e.g., where there is immediate risk to the public health), provided that the order of prohibition states that the comment period and/or effective date have been abbreviated because there are exceptional circumstances, and the order of prohibition sets forth the agency's rationale for taking such action.

(e) If FDA publishes a notice in the FEDERAL REGISTER modifying an order of prohibition, the agency will specify in the modified order of prohibition the nature and extent of the modified prohibition, the reasons for it, and the agency's response to any comments on the original order of prohibition.

(f) A current listing of drugs prohibited for extralabel use in animals will be codified in § 530.41.

(g) After the submission of appropriate information (i.e., adequate data, an acceptable method, approval of a new animal drug application for the prohibited extralabel use, or information demonstrating that the prohibition was based on incorrect data), FDA may, by publication of an appropriate notice in the FEDERAL REGISTER, remove a drug from the list of human and animal drugs prohibited for extralabel use in animals, or may modify a prohibition.

(h) FDA may prohibit extralabel use of a drug in food-producing animals without establishing a safe level.

Subpart D—Extralabel Use of Human and Animal Drugs in Animals Not Intended for Human Consumption

§ 530.30 Extralabel drug use in nonfood animals.

(a) Because extralabel use of animal and human drugs in nonfood-producing animals does not

ordinarily pose a threat to the public health, extralabel use of animal and human drugs is permitted in nonfood-producing animal practice except when the public health is threatened. In addition, the provisions of § 530.20(a)(1) will apply to the use of an approved animal drug.

(b) If FDA determines that an extralabel drug use in animals not intended for human consumption presents a risk to the public health, the agency may publish in the FEDERAL REGISTER a notice prohibiting such use following the procedures in § 530.25. The prohibited extralabel drug use will be codified in § 530.41.

Subpart E—Safe Levels for Extralabel Use of Drugs in Animals and Drugs Prohibited From Extralabel Use in Animals

§ 530.40 Safe levels and availability of analytical methods.

(a) In accordance with § 530.22, the following safe levels for extralabel use of an approved animal drug or human drug have been established: [Reserved]

(b) In accordance with § 530.22, the following analytical methods have been accepted by FDA: [Reserved]

§ 530.41 Drugs prohibited for extralabel use in animals.

(a) The following drugs, families of drugs, and substances are prohibited for extralabel animal and human drug uses in food-producing animals.

(1) Chloramphenicol;

(2) Clenbuterol;

(3) Diethylstilbestrol (DES);

(4) Dimetridazole;

(5) Ipronidazole;

(6) Other nitroimidazoles;

(7) Furazolidone.

(8) Nitrofurazone.

(9) Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine);

(10) Fluoroquinolones; and

(11) Glycopeptides.

(12) Phenylbutazone in female dairy cattle 20 months of age or older.

(13) Cephalosporins (not including cephapirin) in cattle, swine, chickens, or turkeys:

(i) For disease prevention purposes;

(ii) At unapproved doses, frequencies, durations, or routes of administration; or

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(iii) If the drug is not approved for that species and production class.

(b) The following drugs, families of drugs, and substances are prohibited for extralabel animal and human drug uses in nonfood-producing animals: [Reserved]

(c) [Reserved]

(d) The following drugs, or classes of drugs, that are approved for treating or preventing influenza A, are prohibited from extralabel use in chickens, turkeys, and ducks:

(1) Adamantanes.

(2) Neuraminidase inhibitors.

[62 FR 27947, May 22, 1997, as amended at 67 FR 5471, Feb. 6, 2002; 68 FR 9530, Feb. 28, 2003; 68 FR 14134, Mar. 24, 2003; 71 FR 14377, Mar. 22, 2006; 77 FR 745, Jan. 6, 2012]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MOBIC safely and effectively. See full prescribing information for MOBIC.

MOBIC® (meloxicam) tablets, for oral use
MOBIC® (meloxicam) oral suspension
Initial U.S. Approval: 2000

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **MOBIC is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	5/2016
Warnings and Precautions, Cardiovascular Thrombotic Events (5.1)	5/2016
Warnings and Precautions, Heart Failure and Edema (5.5)	5/2016

----------INDICATIONS AND USAGE----------

MOBIC is a non-steroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years of age or older (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1)
- OA (2.2) and RA (2.3):
  - Starting dose: 7.5 mg once daily
  - Dose may be increased to 15 mg once daily
- JRA (2.4):
  - 0.125 mg/kg once daily up to a maximum of 7.5 mg. JRA dosing using the oral suspension should be individualized based on the weight of the child (2.4)
- MOBIC Tablets and MOBIC Suspension are not interchangeable with approved formulations of oral meloxicam even if the total milligram strength is the same (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

- MOBIC (meloxicam) Tablets: 7.5 mg and 15 mg (3)
- MOBIC (meloxicam) Oral Suspension: 7.5 mg/5 mL (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to meloxicam or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of MOBIC in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of MOBIC in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: MOBIC is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue MOBIC at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

----------ADVERSE REACTIONS----------

- Most common (≥5% and greater than placebo) adverse events in adults are diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (6.1)
- Adverse events observed in pediatric studies were similar in nature to the adult clinical trial experience (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking MOBIC with drugs that interfere with hemostasis. Concomitant use of MOBIC and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARBs) or Beta-Blockers: Concomitant use with MOBIC may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with MOBIC in elderly, volume-depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)
- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of MOBIC in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].**
- **MOBIC is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

1.1 Osteoarthritis (OA)

MOBIC is indicated for relief of the signs and symptoms of osteoarthritis [*see Clinical Studies (14.1)*].

1.2 Rheumatoid Arthritis (RA)

MOBIC is indicated for relief of the signs and symptoms of rheumatoid arthritis [*see Clinical Studies (14.1)*].

1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

MOBIC is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of MOBIC and other treatment options before deciding to use MOBIC. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

After observing the response to initial therapy with MOBIC, adjust the dose to suit an individual patient's needs.

In adults, the maximum recommended daily oral dose of MOBIC is 15 mg regardless of formulation. In patients with hemodialysis, a maximum daily dosage of 7.5 mg is recommended [*see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

MOBIC oral suspension 7.5 mg/5 mL or 15 mg/10 mL may be substituted for MOBIC tablets 7.5 mg or 15 mg, respectively.

Shake the oral suspension gently before using.

MOBIC may be taken without regard to timing of meals.

2.2 Osteoarthritis

For the relief of the signs and symptoms of osteoarthritis the recommended starting and maintenance oral dose of MOBIC is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.

2.3 Rheumatoid Arthritis

For the relief of the signs and symptoms of rheumatoid arthritis, the recommended starting and maintenance oral dose of MOBIC is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.

2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

To improve dosing accuracy in smaller weight children, the use of the MOBIC oral suspension is recommended. MOBIC oral suspension is available in the strength of 7.5 mg/5 mL. For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of MOBIC is 0.125 mg/kg once daily up to a maximum of 7.5 mg. There was no additional benefit demonstrated by increasing the dose above 0.125 mg/kg once daily in these clinical trials.

Juvenile Rheumatoid Arthritis dosing using the oral suspension should be individualized based on the weight of the child:

	0.125 mg/kg	
Weight	**Dose (1.5 mg/mL)**	**Delivered dose**
12 kg (26 lb)	1.0 mL	1.5 mg
24 kg (54 lb)	2.0 mL	3.0 mg
36 kg (80 lb)	3.0 mL	4.5 mg
48 kg (106 lb)	4.0 mL	6.0 mg
≥60 kg (132 lb)	5.0 mL	7.5 mg

2.5 Renal Impairment

The use of MOBIC in subjects with severe renal impairment is not recommended.

In patients on hemodialysis, the maximum dosage of MOBIC is 7.5 mg per day *[see Clinical Pharmacology (12.3)]*.

2.6 Non-Interchangeability with Other Formulations of Meloxicam
MOBIC Tablets and MOBIC Suspension have not shown equivalent systemic exposure to other approved formulations of oral meloxicam. Therefore, MOBIC Tablets and MOBIC Suspension are not interchangeable with other formulations of oral meloxicam product even if the total milligram strength is the same. Do not substitute similar dose strengths of MOBIC Tablets or MOBIC Suspension with other formulations of oral meloxicam product.

3 DOSAGE FORMS AND STRENGTHS

MOBIC (meloxicam) Tablets:

- 7.5 mg: pastel yellow, round, biconvex, uncoated tablet containing meloxicam 7.5 mg. Impressed with the Boehringer Ingelheim logo on one side and the letter "M" on the other.

- 15 mg: pastel yellow, oblong, biconvex, uncoated tablet containing meloxicam 15 mg. Impressed with the tablet code "15" on one side and the letter "M" on the other.

MOBIC (meloxicam) Oral Suspension:

- yellowish green tinged viscous suspension containing 7.5 mg meloxicam per 5 mL.

4 CONTRAINDICATIONS

MOBIC is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as meloxicam, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery
Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients
Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of MOBIC in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If MOBIC is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs, including meloxicam, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue MOBIC until a serious GI adverse event is ruled out.

- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Hepatotoxicity
Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including meloxicam.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue MOBIC immediately, and perform a clinical evaluation of the patient [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

5.4 Hypertension
NSAIDs, including MOBIC, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema
The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of meloxicam may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of MOBIC in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If MOBIC is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia
Renal Toxicity
Long-term administration of NSAIDs, including MOBIC, has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The renal effects of MOBIC may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some MOBIC metabolites are excreted by the kidney, monitor patients for signs of worsening renal function.

Correct volume status in dehydrated or hypovolemic patients prior to initiating MOBIC. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of MOBIC [*see Drug Interactions (7)*].

No information is available from controlled clinical studies regarding the use of MOBIC in patients with advanced renal disease. Avoid the use of MOBIC in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If MOBIC is used in patients with advanced renal disease, monitor patients for signs of worsening renal function [*see Clinical Pharmacology (12.3)*].

Hyperkalemia
Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions
Meloxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, MOBIC is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When MOBIC is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
NSAIDs, including meloxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of MOBIC at the first appearance of skin rash or any other sign of hypersensitivity. MOBIC is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Premature Closure of Fetal Ductus Arteriosus
Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including MOBIC, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

5.11 Hematologic Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with MOBIC has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including MOBIC, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.12 Masking of Inflammation and Fever
The pharmacological activity of MOBIC in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Cardiovascular Thrombotic Events [*see Boxed Warning and Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration, and Perforation [*see Boxed Warning and Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults
Osteoarthritis and Rheumatoid Arthritis
The MOBIC Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3505 OA patients and 1351 RA patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo- and/or active-controlled osteoarthritis trials and 2363 of these patients were treated in ten placebo- and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo.

Table 1a depicts adverse events that occurred in ≥2% of the MOBIC treatment groups in a 12-week placebo- and active-controlled osteoarthritis trial.

Table 1b depicts adverse events that occurred in ≥2% of the MOBIC treatment groups in two 12-week placebo-controlled rheumatoid arthritis trials.

Table 1a Adverse Events (%) Occurring in ≥2% of MOBIC Patients in a 12-Week Osteoarthritis Placebo- and Active-Controlled Trial

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 100 mg daily
No. of Patients	**157**	**154**	**156**	**153**
Gastrointestinal	17.2	20.1	17.3	28.1
Abdominal pain	2.5	1.9	2.6	1.3
Diarrhea	3.8	7.8	3.2	9.2
Dyspepsia	4.5	4.5	4.5	6.5
Flatulence	4.5	3.2	3.2	3.9
Nausea	3.2	3.9	3.8	7.2
Body as a Whole				
Accident household	1.9	4.5	3.2	2.6
Edema[1]	2.5	1.9	4.5	3.3
Fall	0.6	2.6	0.0	1.3
Influenza-like symptoms	5.1	4.5	5.8	2.6
Central and Peripheral Nervous System				
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
Respiratory				
Pharyngitis	1.3	0.6	3.2	1.3
Upper respiratory tract infection	1.9	3.2	1.9	3.3
Skin				
Rash[2]	2.5	2.6	0.6	2.0

[1] WHO preferred terms edema, edema dependent, edema peripheral, and edema legs combined

[2] WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

Table 1b Adverse Events (%) Occurring in ≥2% of MOBIC Patients in two 12-Week Rheumatoid Arthritis Placebo-Controlled Trials

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily
No. of Patients	**469**	**481**	**477**
Gastrointestinal Disorders	14.1	18.9	16.8
Abdominal pain NOS[2]	0.6	2.9	2.3
Dyspeptic signs and symptoms[1]	3.8	5.8	4.0
Nausea[2]	2.6	3.3	3.8
General Disorders and Administration Site Conditions			
Influenza-like illness[2]	2.1	2.9	2.3
Infection and Infestations			
Upper respiratory tract infections-pathogen class unspecified[1]	4.1	7.0	6.5
Musculoskeletal and Connective Tissue Disorders			
Joint related signs and symptoms[1]	1.9	1.5	2.3
Nervous System Disorders			
Headaches NOS[2]	6.4	6.4	5.5
Skin and Subcutaneous Tissue Disorders			
Rash NOS[2]	1.7	1.0	2.1

[1] MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling)

[2] MedDRA preferred term: nausea, abdominal pain NOS, influenza-like illness, headaches NOS, and rash NOS

The adverse events that occurred with MOBIC in ≥2% of patients treated short-term (4 to 6 weeks) and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 2.

Table 2 Adverse Events (%) Occurring in ≥2% of MOBIC Patients in 4 to 6 Weeks and 6 Month Active-Controlled Osteoarthritis Trials

	4 to 6 Weeks Controlled Trials		6 Month Controlled Trials	
	MOBIC 7.5 mg daily	**MOBIC 15 mg daily**	**MOBIC 7.5 mg daily**	**MOBIC 15 mg daily**
No. of Patients	**8955**	**256**	**169**	**306**
Gastrointestinal	11.8	18.0	26.6	24.2
Abdominal pain	2.7	2.3	4.7	2.9
Constipation	0.8	1.2	1.8	2.6
Diarrhea	1.9	2.7	5.9	2.6
Dyspepsia	3.8	7.4	8.9	9.5
Flatulence	0.5	0.4	3.0	2.6
Nausea	2.4	4.7	4.7	7.2
Vomiting	0.6	0.8	1.8	2.6
Body as a Whole				
Accident household	0.0	0.0	0.6	2.9
Edema[1]	0.6	2.0	2.4	1.6
Pain	0.9	2.0	3.6	5.2
Central and Peripheral Nervous System				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
Hematologic				
Anemia	0.1	0.0	4.1	2.9
Musculoskeletal				
Arthralgia	0.5	0.0	5.3	1.3
Back pain	0.5	0.4	3.0	0.7
Psychiatric				
Insomnia	0.4	0.0	3.6	1.6
Respiratory				
Coughing	0.2	0.8	2.4	1.0

Upper respiratory tract infection	0.2	0.0	8.3	7.5
Skin				
Pruritus	0.4	1.2	2.4	0.0
Rash[2]	0.3	1.2	3.0	1.3
Urinary				
Micturition frequency	0.1	0.4	2.4	1.3
Urinary tract infection	0.3	0.4	4.7	6.9

[1] WHO preferred terms edema, edema dependent, edema peripheral, and edema legs combined

[2] WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore, the daily dose of MOBIC should not exceed 15 mg.

Pediatrics

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Three hundred and eighty-seven patients with pauciarticular and polyarticular course JRA were exposed to MOBIC with doses ranging from 0.125 to 0.375 mg/kg per day in three clinical trials. These studies consisted of two 12-week multicenter, double-blind, randomized trials (one with a 12-week open-label extension and one with a 40-week extension) and one 1-year open-label PK study. The adverse events observed in these pediatric studies with MOBIC were similar in nature to the adult clinical trial experience, although there were differences in frequency. In particular, the following most common adverse events, abdominal pain, vomiting, diarrhea, headache, and pyrexia, were more common in the pediatric than in the adult trials. Rash was reported in seven (<2%) patients receiving MOBIC. No unexpected adverse events were identified during the course of the trials. The adverse events did not demonstrate an age or gender-specific subgroup effect.

The following is a list of adverse drug reactions occurring in <2% of patients receiving MOBIC in clinical trials involving approximately 16,200 patients.

Body as a Whole	allergic reaction, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase
Cardiovascular	angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis
Central and Peripheral Nervous System	convulsions, paresthesia, tremor, vertigo
Gastrointestinal	colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative
Heart Rate and Rhythm	arrhythmia, palpitation, tachycardia
Hematologic	leukopenia, purpura, thrombocytopenia
Liver and Biliary System	ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis
Metabolic and Nutritional	dehydration
Psychiatric	abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence
Respiratory	asthma, bronchospasm, dyspnea
Skin and Appendages	alopecia, angioedema, bullous eruption, photosensitivity reaction, pruritus, sweating increased, urticaria
Special Senses	abnormal vision, conjunctivitis, taste perversion, tinnitus
Urinary System	albuminuria, BUN increased, creatinine increased, hematuria, renal failure

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of MOBIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. Adverse reactions reported in worldwide post marketing experience or the literature include: acute urinary retention; agranulocytosis; alterations in mood (such as mood elevation); anaphylactoid reactions including shock; erythema multiforme; exfoliative dermatitis; interstitial nephritis; jaundice; liver failure; Stevens-Johnson syndrome; toxic epidermal necrolysis, and infertility female.

7 DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with meloxicam. See also *Warnings and Precautions (5.2, 5.6, 5.11) and Clinical Pharmacology (12.3).*

Table 3 Clinically Significant Drug Interactions with Meloxicam

Drugs that Interfere with Hemostasis	
Clinical Impact:	• Meloxicam and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of meloxicam and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.

	• Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of MOBIC with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.11)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of MOBIC and low dose aspirin or analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.11)*]. MOBIC is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, or Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of MOBIC and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of MOBIC and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. However, studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam.
Intervention:	During concomitant use of MOBIC with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis [*see Clinical Pharmacology (12.3)*].
Intervention:	During concomitant use of MOBIC and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of MOBIC and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of MOBIC and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of MOBIC and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*].
Intervention:	The concomitant use of meloxicam with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of MOBIC and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of MOBIC and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. Patients taking meloxicam should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration. In patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with pemetrexed is not recommended.
Kayexalate® (sodium polystyrene sulfonate)	
Clinical Impact:	Cases of intestinal necrosis (possibly fatal) have been described in patients who received concomitant sorbitol and Kayexalate® (sodium polystyrene sulfonate). Due to the presence of sorbitol in MOBIC Oral Suspension, use with Kayexalate® is not recommended.
Intervention:	The concomitant use of MOBIC Oral Suspension with Kayexalate® is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including MOBIC, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including MOBIC, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Warnings and Precautions (5.10)*].

There are no adequate and well-controlled studies of MOBIC in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss.

In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of MOBIC. Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times MRHD of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD *[see Data]*.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of MOBIC during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Animal Data

Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of MOBIC based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion). In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65- and 6.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.08-times MRHD based on BSA comparison).

8.2 Lactation

Risk Summary

There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOBIC and any potential adverse effects on the breastfed infant from the MOBIC or from the underlying maternal condition.

Data

Animal data

Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including MOBIC, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including MOBIC, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

The safety and effectiveness of meloxicam in pediatric JRA patients from 2 to 17 years of age has been evaluated in three clinical trials [*see Dosage and Administration (2.3), Adverse Reactions (6.1) and Clinical Studies (14.2)*].

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)*].

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been adequately studied. Since meloxicam is significantly metabolized in the liver and hepatotoxicity may occur, use meloxicam with caution in patients with hepatic impairment [*see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been studied. The use of MOBIC in subjects with severe renal impairment is not recommended. In patients on hemodialysis, meloxicam should not exceed 7.5 mg per day. Meloxicam is not dialyzable [*see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

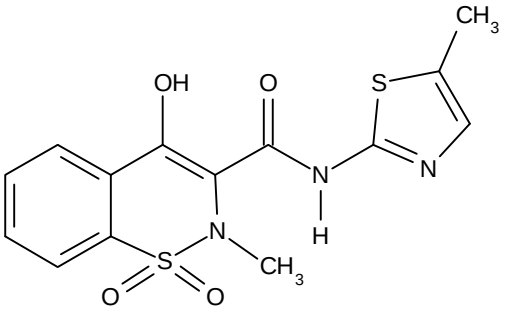
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

There is limited experience with meloxicam overdosage. Cholestyramine is known to accelerate the clearance of meloxicam. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdosage.

For additional information about overdosage treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION

MOBIC (meloxicam) is a nonsteroidal anti-inflammatory drug (NSAID). Each pastel yellow MOBIC tablet contains 7.5 mg or 15 mg meloxicam for oral administration. Each bottle of MOBIC oral suspension contains 7.5 mg meloxicam per 5 mL. Meloxicam is chemically designated as 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is $C_{14}H_{13}N_3O_4S_2$ and it has the following structural formula:



Meloxicam is a pastel yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient $(\log P)_{app}$ = 0.1 in *n*-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.

MOBIC is available as a tablet for oral administration containing 7.5 mg or 15 mg meloxicam, and as an oral suspension containing 7.5 mg meloxicam per 5 mL.

The inactive ingredients in MOBIC tablets include colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium citrate dihydrate.

The inactive ingredients in MOBIC oral suspension include colloidal silicon dioxide, hydroxyethylcellulose, sorbitol, glycerol, xylitol, monobasic sodium phosphate (dihydrate), saccharin sodium, sodium benzoate, citric acid (monohydrate), raspberry flavor, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meloxicam has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of MOBIC, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Meloxicam is a potent inhibitor of prostaglandin synthesis *in vitro*. Meloxicam concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean C_{max} was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady-state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

Meloxicam oral suspension doses of 7.5 mg/5 mL and 15 mg/10 mL have been found to be bioequivalent to meloxicam 7.5 mg and 15 mg capsules, respectively. Meloxicam capsules have been shown to be bioequivalent to MOBIC tablets.

Table 4 Single Dose and Steady-State Pharmacokinetic Parameters for Oral 7.5 mg and 15 mg Meloxicam (Mean and % CV)[1]

Pharmacokinetic Parameters (% CV)		Steady State			Single Dose	
		Healthy male adults (Fed)[2]	Elderly males (Fed)[2]	Elderly females (Fed)[2]	Renal failure (Fasted)	Hepatic insufficiency (Fasted)
		7.5 mg[3] tablets	15 mg capsules	15 mg capsules	15 mg capsules	15 mg capsules
N		18	5	8	12	12
C_{max}	[µg/mL]	1.05 (20)	2.3 (59)	3.2 (24)	0.59 (36)	0.84 (29)
t_{max}	[h]	4.9 (8)	5 (12)	6 (27)	4 (65)	10 (87)
$t_{1/2}$	[h]	20.1 (29)	21 (34)	24 (34)	18 (46)	16 (29)

CL/f	[mL/min]	8.8 (29)	9.9 (76)	5.1 (22)	19 (43)	11 (44)
V_Z/f[4]	[L]	14.7 (32)	15 (42)	10 (30)	26 (44)	14 (29)

[1] The parameter values in the table are from various studies
[2] not under high fat conditions
[3] MOBIC tablets
[4] $V_Z/f = Dose/(AUC \cdot K_{el})$

Food and Antacid Effects
Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (i.e., C_{max}) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (T_{max}) was achieved between 5 and 6 hours. In comparison, neither the AUC nor the C_{max} values for meloxicam suspension were affected following a similar high fat meal, while mean T_{max} values were increased to approximately 7 hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. Based on these results, MOBIC can be administered without regard to timing of meals or concomitant administration of antacids.

Distribution
The mean volume of distribution (Vss) of meloxicam is approximately 10 L. Meloxicam is ~99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to ~99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam.

Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of this penetration is unknown.

Elimination
Metabolism
Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). *In vitro* studies indicate that CYP2C9 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively. All the four metabolites are not known to have any *in vivo* pharmacological activity.

Excretion
Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6%, and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.

The mean elimination half-life ($t_{1/2}$) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range. Plasma clearance ranges from 7 to 9 mL/min.

Specific Populations
Pediatric
After single (0.25 mg/kg) dose administration and after achieving steady state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger patients (2 to 6 years old) as compared to the older patients (7 to 16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized to a dose of 0.25 mg/kg [*see Dosage and Administration (2.4)*]. The meloxicam mean (SD) elimination half-life was 15.2 (10.1) and 13.0 hours (3.0) for the 2 to 6 year old patients, and 7 to 16 year old patients, respectively.

In a covariate analysis, utilizing population pharmacokinetics body-weight, but not age, was the single predictive covariate for differences in the meloxicam apparent oral plasma clearance. The body-weight normalized apparent oral clearance values were adequate predictors of meloxicam exposure in pediatric patients.

The pharmacokinetics of MOBIC in pediatric patients under 2 years of age have not been investigated.

Geriatric
Elderly males (≥65 years of age) exhibited meloxicam plasma concentrations and steady-state pharmacokinetics similar to young males. Elderly females (≥65 years of age) had a 47% higher AUC_{ss} and 32% higher $C_{max,ss}$ as compared to younger females (≤55 years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

Sex
Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg MOBIC, the mean elimination half-life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 hours vs 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the C_{max} or T_{max} across genders.

Hepatic Impairment
Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)*].

Renal Impairment
Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all groups. The higher meloxicam clearance in

subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of MOBIC in subjects with severe renal impairment is not recommended [*see Dosage and Administration (2.5),Warnings and Precautions (5.6) and Use in Specific Populations (8.7)*].

Hemodialysis
Following a single dose of meloxicam, the free C_{max} plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable [*see Dosage and Administration (2.1) and Use in Specific Populations (8.7)*].

Drug Interaction Studies
Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. When MOBIC is administered with aspirin (1000 mg three times daily) to healthy volunteers, it tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

Cholestyramine: Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in $t_{1/2}$, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

Cimetidine: Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

Digoxin: Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after β-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Lithium: In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg twice daily with meloxicam 15 mg QD every day as compared to subjects receiving lithium alone [*see Drug Interactions (7)*].

Methotrexate: A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. *In vitro*, methotrexate did not displace meloxicam from its human serum binding sites [*see Drug Interactions (7)*].

Warfarin: The effect of meloxicam on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering MOBIC with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
There was no increase in tumor incidence in long-term carcinogenicity studies in rats (104 weeks) and mice (99 weeks) administered meloxicam at oral doses up to 0.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 0.5- and 2.6-times, respectively, the maximum recommended human dose [MRHD] of 15 mg/day MOBIC based on body surface area [BSA] comparison).

Mutagenesis
Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Impairment of Fertility
Meloxicam did not impair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 5.8- and 3.2-times greater, respectively, than the MRHD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Osteoarthritis and Rheumatoid Arthritis

The use of MOBIC for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in a 12-week, double-blind, controlled trial. MOBIC (3.75 mg, 7.5 mg, and 15 mg daily) was compared to placebo. The four primary endpoints were investigator's global assessment, patient global assessment, patient pain assessment, and total WOMAC score (a self-administered questionnaire addressing pain, function, and stiffness). Patients on MOBIC 7.5 mg daily and MOBIC 15 mg daily showed significant improvement in each of these endpoints compared with placebo.

The use of MOBIC for the management of signs and symptoms of osteoarthritis was evaluated in six double-blind, active-controlled trials outside the U.S. ranging from 4 weeks' to 6 months' duration. In these trials, the efficacy of MOBIC, in doses of 7.5 mg/day and 15 mg/day, was comparable to piroxicam 20 mg/day and diclofenac SR 100 mg/day and consistent with the efficacy seen in the U.S. trial.

The use of MOBIC for the treatment of the signs and symptoms of rheumatoid arthritis was evaluated in a 12-week, double-blind, controlled multinational trial. MOBIC (7.5 mg, 15 mg, and 22.5 mg daily) was compared to placebo. The primary endpoint in this study was the ACR20 response rate, a composite measure of clinical, laboratory, and functional measures of RA response. Patients receiving MOBIC 7.5 mg and 15 mg daily showed significant improvement in the primary endpoint compared with placebo. No incremental benefit was observed with the 22.5 mg dose compared to the 15 mg dose.

14.2 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

The use of MOBIC for the treatment of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older was evaluated in two 12-week, double-blind, parallel-arm, active-controlled trials.

Both studies included three arms: naproxen and two doses of meloxicam. In both studies, meloxicam dosing began at 0.125 mg/kg/day (7.5 mg maximum) or 0.25 mg/kg/day (15 mg maximum), and naproxen dosing began at 10 mg/kg/day. One study used these doses throughout the 12-week dosing period, while the other incorporated a titration after 4 weeks to doses of 0.25 mg/kg/day and 0.375 mg/kg/day (22.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen.

The efficacy analysis used the ACR Pediatric 30 responder definition, a composite of parent and investigator assessments, counts of active joints and joints with limited range of motion, and erythrocyte sedimentation rate. The proportion of responders were similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

MOBIC is available as a pastel yellow, round, biconvex, uncoated tablet containing meloxicam 7.5 mg or as a pastel yellow, oblong, biconvex, uncoated tablet containing meloxicam 15 mg. The 7.5 mg tablet is impressed with the Boehringer Ingelheim logo on one side, and on the other side, the letter “M”. The 15 mg tablet is impressed with the tablet code “15” on one side and the letter “M” on the other. MOBIC is also available as a yellowish green tinged viscous oral suspension containing 7.5 mg meloxicam in 5 mL.

MOBIC (meloxicam) tablets 7.5 mg: NDC 0597-0029-01; Bottles of 100

MOBIC (meloxicam) tablets 15 mg: NDC 0597-0030-01; Bottles of 100

MOBIC (meloxicam) oral suspension 7.5 mg/5 mL: NDC 0597-0034-01; Bottles of 100 mL

Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep MOBIC tablets in a dry place.

Dispense tablets in a tight container. Keep oral suspension container tightly closed.

Keep this and all medications out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed.

Inform patients, families or their caregivers of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their healthcare provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop MOBIC and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

Heart Failure and Edema
Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions
Advise patients to stop MOBIC immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9)*].

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including MOBIC, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity
Inform pregnant women to avoid use of MOBIC and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of MOBIC with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with MOBIC until they talk to their healthcare provider [*see Drug Interactions (7)*].

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For current prescribing information, scan the code below or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or TTY 1-800-459-9906.

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090340141/10
OT1407JE042016

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- new or worse high blood pressure
- heart failure

- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs:

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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090340141/10
OT1407JE042016

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2016

Appendix 17

Print Feedback Export to File

Search:

Search

Citation

Tags

HERO ID
7564813

Reference Type
Journal Article

Title
A New Insight into Meloxicam: Assessment of Antioxidant and Anti-Glycating Activity in In Vitro Studies

Author(s)
Pawlukianiec, C; Gryciuk, ME; Mil, KM; Żendzian-Piotrowska, M; Zalewska, A; Maciejczyk, M

Year
2020

Is Peer Reviewed?
1

Journal
Pharmaceuticals
ISSN: *1424-8247*

Volume
13

Issue
9

Language
English

PMID
32927809

DOI
10.3390/ph13090240

Abstract

Appendix 17

Meloxicam is a non-steroidal anti-inflammatory drug, which has a preferential inhibitory effect to cyclooxyganase-2 (COX-2). Although the drug inhibits prostaglandin synthesis, the exact mechanism of meloxicam is still unknown. This is the first study to assess the effect of meloxicam on protein glyco-oxidation as well as antioxidant activity. For this purpose, we used an in vitro model of oxidized bovine serum albumin (BSA). Glucose, fructose, ribose, glyoxal and methylglyoxal were used as glycating agents, while chloramine T was used as an oxidant. We evaluated the antioxidant properties of albumin (2,2-di-phenyl-1-picrylhydrazyl radical scavenging capacity, total antioxidant capacity and ferric reducing antioxidant power), the intensity of protein glycation (Amadori products, advanced glycation end products) and glyco-oxidation (dityrosine, kynurenine, N-formylkynurenine, tryptophan and amyloid-β) as well as the content of protein oxidation products (advanced oxidation protein products, carbonyl groups and thiol groups). We have demonstrated that meloxicam enhances the antioxidant properties of albumin and prevents the protein oxidation and glycation under the influence of various factors such as sugars, aldehydes and oxidants. Importantly, the antioxidant and anti-glycating activity is similar to that of routinely used antioxidants such as captopril, Trolox, reduced glutathione and lipoic acid as well as protein glycation inhibitors (aminoguanidine). Pleiotropic action of meloxicam may increase the effectiveness of anti-inflammatory treatment in diseases with oxidative stress etiology.

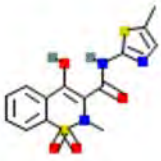
LAST UPDATED ON NOVEMBER 22, 2023

Appendix 18

National Library of Medicine
National Center for Biotechnology Information

COMPOUND SUMMARY > LCSS

Meloxicam

PubChem CID	54677470
Structure	 2D
Synonyms	meloxicam 71125-38-7 Mobic Metacam Movalis
Molecular Formula	$C_{14}H_{13}N_3O_4S_2$
Molecular Weight	351.4 g/mol *Computed by PubChem 2.1 (PubChem release 2021.05.07)*

1 GHS Classification

1 of 2 View All

Pictogram(s)

Acute Toxic Health Hazard

Appendix 18

Signal	Danger
GHS Hazard Statements	H301 (97.39%): Toxic if swallowed [Danger Acute toxicity, oral] H360 (51.3%): May damage fertility or the unborn child [Danger Reproductive toxicity] H412 (57.39%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
Precautionary Statement Codes	P203, P264, P270, P273, P280, P301+P316, P318, P321, P330, P405, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)
ECHA C&L Notifications Summary	*Aggregated GHS information provided by 116 companies from 21 notifications to the ECHA C&L Inventory. Each notification may be associated with multiple companies.* *Reported as not meeting GHS hazard criteria by 1 of 116 companies. For more detailed information, please visit ECHA C&L website.* *Of the 20 notification(s) provided by 115 of 116 companies with hazard statement code(s).* *Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.*

Appendix 18

▾ European Chemicals Agency (ECHA)

Source	European Chemicals Agency (ECHA)
Record Name	Meloxicam
URL	https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/34167
Description	The information provided here is aggregated from the "Notified classification and labelling" from ECHA's C&L Inventory. Read more: https://echa.europa.eu/information-on-chemicals/cl-inventory-database
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2 Identifiers

2.1 CAS

71125-38-7

▾ CAS Common Chemistry; ChemIDplus; DrugBank; EPA DSSTox; European Chemicals Agency (ECH...

Source	CAS Common Chemistry
Record Name	Meloxicam
URL	https://commonchemistry.cas.org/detail?cas_rn=71125-38-7
Description	CAS Common Chemistry is an open community resource for accessing chemical information. Nearly 500,000 chemical substances from CAS REGISTRY cover areas of community interest, including common and frequently regulated chemicals, and those relevant to high school and undergraduate chemistry classes. This chemical information, curated by our expert scientists, is provided in alignment with our mission as a division of the American Chemical Society.
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Appendix 18

Source	ChemIDplus
Record Name	Meloxicam [USAN:USP:INN:BAN]
URL	https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0071125387
Description	ChemIDplus is a free, web search system that provides access to the structure and nomenclature authority files used for the identification of chemical substances cited in National Library of Medicine (NLM) databases, including the TOXNET system.
License	https://www.nlm.nih.gov/copyright.html

Source	DrugBank
Record Name	Meloxicam
URL	https://www.drugbank.ca/drugs/DB00814
Description	The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.
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Source	EPA DSSTox
Record Name	Meloxicam
URL	https://comptox.epa.gov/dashboard/DTXSID1020803
Description	DSSTox provides a high quality public chemistry resource for supporting improved predictive toxicology.
License	https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Source	European Chemicals Agency (ECHA)
Record Name	2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide
URL	https://echa.europa.eu/substance-information/-/substanceinfo/100.113.257
Description	The European Chemicals Agency (ECHA) is an agency of the European Union which is the driving force among regulatory authorities in implementing the EU's groundbreaking chemicals legislation for the benefit of human health and the environment as well as for innovation and competitiveness.

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Source	FDA Global Substance Registration System (GSRS)
Record Name	MELOXICAM
URL	https://gsrs.ncats.nih.gov/ginas/app/beta/substances/VG2QF83CGL
Description	The FDA Global Substance Registration System (GSRS) enables the efficient and accurate exchange of information on what substances are in regulated products. Instead of relying on names, which vary across regulatory domains, countries, and regions, the GSRS knowledge base makes it possible for substances to be defined by standardized, scientific descriptions.
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Source	Hazardous Substances Data Bank (HSDB)
Record Name	Meloxicam
URL	https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741
Description	The Hazardous Substances Data Bank (HSDB) is a toxicology database that focuses on the toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB has been assessed by a Scientific Review Panel.
License	https://www.nlm.nih.gov/web_policies.html

Source	Human Metabolome Database (HMDB)
Record Name	Meloxicam
URL	http://www.hmdb.ca/metabolites/HMDB0014952

Appendix 18

Description	The Human Metabolome Database (HMDB) is a freely available electronic database containing detailed information about small molecule metabolites found in the human body.
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2.2 InChI

InChI=1S/C14H13N3O4S2/c1-8-7-15-14(22-8)16-13(19)11-12(18)9-5-3-4-6-10(9)23(20,21)17(11)2/h3-7,18H,1-2H3,(H,15,16,19)

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

Source	PubChem
URL	https://pubchem.ncbi.nlm.nih.gov
Description	Data deposited in or computed by PubChem

2.3 InChIKey

ZRVUJXDFFKFLMG-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

Source	PubChem
URL	https://pubchem.ncbi.nlm.nih.gov
Description	Data deposited in or computed by PubChem

3 Physical Properties

Appendix 18

3.1 Physical Description

Solid

▾ Human Metabolome Database (HMDB)

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URL	http://www.hmdb.ca/metabolites/HMDB0014952
Description	The Human Metabolome Database (HMDB) is a freely available electronic database containing detailed information about small molecule metabolites found in the human body.
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3.2 Boiling Point

581.3±60.0

https://www.chemsrc.com/en/cas/71125-38-7_1083007.html

▾ DrugBank

Source	DrugBank
Record Name	Meloxicam
URL	https://www.drugbank.ca/drugs/DB00814
Description	The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.
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Appendix 18

3.3 Melting Point

256

http://www.guildlink.com.au/gc/ws/by/pi.cfm?product=bypmobic10517

▾ DrugBank

Source	DrugBank
Record Name	Meloxicam
URL	https://www.drugbank.ca/drugs/DB00814
Description	The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.
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254 °C (decomposes)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1006

▾ Hazardous Substances Data Bank (HSDB)

Source	Hazardous Substances Data Bank (HSDB)
Record Name	Meloxicam
URL	https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741
Description	The Hazardous Substances Data Bank (HSDB) is a toxicology database that focuses on the toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB has been assessed by a Scientific Review Panel.
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254 °C

▾ Human Metabolome Database (HMDB)

Source	Human Metabolome Database (HMDB)

Appendix 18

Record Name	Meloxicam
URL	http://www.hmdb.ca/metabolites/HMDB0014952
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View Less...

3.4 Solubility

48.7 [ug/mL] (The mean of the results at pH 7.4)

▾ Burnham Center for Chemical Genomics

Source	Burnham Center for Chemical Genomics
Record Name	SID50085983
URL	https://pubchem.ncbi.nlm.nih.gov/bioassay/1996#section=Data-Table
Description	Aqueous solubility in buffer at pH 7.4

22mg/ml

https://www.chemicalbook.com/ChemicalProductProperty_US_CB2191355.aspx

▾ DrugBank

Source	DrugBank
Record Name	Meloxicam
URL	https://www.drugbank.ca/drugs/DB00814
Description	The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.

Appendix 18

License	Creative Common's Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/legalcode) https://www.drugbank.ca/legal/terms_of_use

Very slightly soluble in methanol. Practically insoluble in water, with higher solubility observed in strong acids and bases.

Wishart DS et al; DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 1;34. Available from, as of Apr 23, 2009: https://www.drugbank.ca

▾ Hazardous Substances Data Bank (HSDB)

Source	Hazardous Substances Data Bank (HSDB)
Record Name	Meloxicam
URL	https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741
Description	The Hazardous Substances Data Bank (HSDB) is a toxicology database that focuses on the toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB has been assessed by a Scientific Review Panel.
License	https://www.nlm.nih.gov/web_policies.html

1.54e-01 g/L

▾ Human Metabolome Database (HMDB)

Source	Human Metabolome Database (HMDB)
Record Name	Meloxicam
URL	http://www.hmdb.ca/metabolites/HMDB0014952
Description	The Human Metabolome Database (HMDB) is a freely available electronic database containing detailed information about small molecule metabolites found in the human body.
License	HMDB is offered to the public as a freely available resource. Use and re-distribution of the data, in whole or in part, for commercial purposes requires explicit permission of the authors and explicit acknowledgment of the source material (HMDB) and the original publication (see the HMDB citing page). We ask that users who download significant portions of the database cite the HMDB paper in any resulting publications. http://www.hmdb.ca/citing

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4 Storage and Handling

4.1 Storage Conditions

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

US Natl Inst Health; DailyMed. Current Medication Information for Meloxicam (meloxicam) tablets (September 2007). Available from, as of June 29, 2009: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5437

▼ Hazardous Substances Data Bank (HSDB)

Source	Hazardous Substances Data Bank (HSDB)
Record Name	Meloxicam
URL	https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741
Description	The Hazardous Substances Data Bank (HSDB) is a toxicology database that focuses on the toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB has been assessed by a Scientific Review Panel.
License	https://www.nlm.nih.gov/web_policies.html

5 Cleanup and Disposal

5.1 Disposal Methods

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.

▼ Hazardous Substances Data Bank (HSDB)

Source	Hazardous Substances Data Bank (HSDB)
Record Name	Meloxicam
URL	https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741
Description	The Hazardous Substances Data Bank (HSDB) is a toxicology database that focuses on the toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures,

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	environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB has been assessed by a Scientific Review Panel.
License	https://www.nlm.nih.gov/web_policies.html

6 Information Sources

FILTER BY SOURCE

ALL SOURCES

1. ## Burnham Center for Chemical Genomics

SID50085983

https://pubchem.ncbi.nlm.nih.gov/bioassay/1996#section=Data-Table

2. ## DrugBank

LICENSE
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https://www.drugbank.ca/legal/terms_of_use

Meloxicam

https://www.drugbank.ca/drugs/DB00814

3. ## Hazardous Substances Data Bank (HSDB)

LICENSE
https://www.nlm.nih.gov/web_policies.html

Meloxicam

https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7741

4. ## Human Metabolome Database (HMDB)

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http://www.hmdb.ca/citing

Meloxicam

http://www.hmdb.ca/metabolites/HMDB0014952

5. ## CAS Common Chemistry

LICENSE
The data from CAS Common Chemistry is provided under a CC-BY-NC 4.0 license, unless otherwise stated.

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Meloxicam

https://commonchemistry.cas.org/detail?cas_rn=71125-38-7

6. ChemIDplus

Meloxicam [USAN:USP:INN:BAN]

https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0071125387

7. EPA DSSTox

Meloxicam

https://comptox.epa.gov/dashboard/DTXSID1020803

8. European Chemicals Agency (ECHA)

2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide

https://echa.europa.eu/substance-information/-/substanceinfo/100.113.257

Meloxicam

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/34167

9. FDA Global Substance Registration System (GSRS)

MELOXICAM

https://gsrs.ncats.nih.gov/ginas/app/beta/substances/VG2QF83CGL

10. Hazardous Chemical Information System (HCIS), Safe Work Australia

Meloxicam

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http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=2814

11. PubChem

https://pubchem.ncbi.nlm.nih.gov

Cite Download

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Appendix 19

Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA)

Extralabel Use of FDA Approved Drugs in Animals
Limitations to Extralabel Use Provisions of AMDUCA
Extralabel Use in Food-Producing Animals
Labeling of Drugs Prescribed for Extralabel Use
Prohibitions Under AMDUCA
Compounding Under AMDUCA
Additional Information

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals under certain conditions. Extralabel use refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. Under AMDUCA and its implementing regulations published at Title 21, Code of Federal Regulations, Part 530 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530) (21 CFR 530), any extralabel use of an approved new animal or human drug must be by or on the lawful order of a veterinarian within the context of a veterinarian-client-patient relationship (VCPR). Extralabel use must also comply with other provisions of 21 CFR 530. A list of drugs specifically prohibited from extralabel use appears in 21 CFR 530.41.

Extralabel Use of FDA Approved Drugs in Animals

"Extralabel use" is defined as:

"Actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses." (21 CFR 530.3(a))

Under the provisions of 21 CFR 530, the FDA recognizes the professional judgment of veterinarians, and permits the extralabel use of drugs by veterinarians under certain conditions. Extralabel use of drugs may only take place within the scope of a valid VCPR. In the absence of a valid VCPR, if an approved new animal drug is used for a use for which it is

not labeled, such use has caused the drug to be deemed unsafe under the Federal Food, Drug and Cosmetic Act ("the Act") (21 U.S.C. 360b), and therefore adulterated under the Act (21 U.S.C. 351(a)(5)).

An approved animal drug or approved human drug intended to be used for an extralabel use in an animal, other than a use in or on animal feed, is not unsafe under the Act (21 U.S.C. 360b) and is exempt from the labeling requirements under the Act (21 U.S.C. 502(f)), if such use is by or on the lawful written or oral order of a licensed veterinarian within the context of a valid VCPR and such use complies with the extralabel use regulation (21 CFR 530). Extralabel use is limited to circumstances when the health of an animal is threatened, or suffering or death may result from failure to treat. This means that extralabel use to enhance production is not permitted.

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Limitations to Extralabel Use Provisions of AMDUCA

In addition to uses which do not comply with the conditions for permitted extralabel use set forth in 21 CFR 530, the following specific extralabel uses included in 21 CFR 530.11 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.11) are not permitted and result in the drug being deemed unsafe within the meaning of section 512 of the Act (21 U.S.C. 360b):

1. Extralabel use in an animal of an approved new animal drug or human drug by a lay person (except when under the supervision of a licensed veterinarian);
2. Extralabel use of an approved new animal drug or human drug in or on an animal feed;
3. Extralabel use resulting in any residue which may present a risk to the public health; and
4. Extralabel use resulting in any residue above an established safe level, safe concentration, or tolerance.

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Extralabel Use in Food-Producing Animals

There are additional specific conditions that must be met for extralabel use of approved animal and approved human drugs in food-producing animals. The following conditions appear in 21 CFR 530.20 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.20):

1. There is no approved animal drug that is labeled for such use and that contains the

same active ingredient in the required dosage form and concentration, except where a veterinarian finds, within the context of a valid VCPR, that the approved animal drug is clinically ineffective for its intended use.

2. Before prescribing or dispensing an approved animal drug or approved human drug for an extralabel use in food animals, the veterinarian must:
    - Make a careful diagnosis and evaluation of the conditions for which the drug is to be used;
    - Establish a substantially extended withdrawal period prior to marketing of milk, meat, eggs, or other edible products supported by appropriate scientific information, if applicable;
    - Institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and
    - Take appropriate measures to assure that assigned time frames for withdrawal are met and no illegal drug residues occur in any food producing animal subjected to extra-label treatment.

The following additional conditions must be met for a permitted extralabel use, in food producing animals, of an approved human drug, or of an animal drug approved only for use in animals not intended for human consumption:

1. Such use must be accomplished in accordance with an appropriate medical rationale; and
2. If scientific information on the human food safety aspect of the use of the drug in food producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply.

Extralabel use of an approved human drug in a food producing animal is not permitted if an animal drug approved for use in food producing animals can be used in an extralabel manner for the particular use.

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Labeling of Drugs Prescribed for Extralabel Use

Any drug prescribed and dispensed for extralabel use by a veterinarian or dispensed by a pharmacist on the order of a veterinarian must bear or be accompanied by labeling information adequate to assure the safe and proper use of the drug. (21 CFR 530.12 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.12)) At a minimum, such information shall include the following:

1. The name and address of the prescribing veterinarian. If the drug is dispensed by a pharmacy on the order of a veterinarian, the labeling shall include the name of the prescribing veterinarian and the name and address of the dispensing pharmacy, and may include the address of the prescribing veterinarian.
2. The established name of the drug (active ingredient), or, if formulated from more than one active ingredient, the established name of each ingredient.
3. Any directions for use specified by the veterinarian (including class/species or identification of the animal(s) being treated; dosage, frequency, and route of administration; and the duration of therapy).
4. Any cautionary statements; and
5. The veterinarian's specified withdrawal, withholding, or discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s).

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Prohibitions Under AMDUCA

Under the AMDUCA provisions, FDA has the right to prohibit extralabel uses of certain drugs in animals.

FDA may prohibit the extralabel use of an approved animal drug or approved human drug or class of drugs in food-producing animals if FDA determines that:

1. An acceptable analytical method needs to be established and such method has not been established or cannot be established; or
2. The extralabel use of the drug or class of drugs presents a risk to the public health.

A prohibition may be a general ban on the extralabel use of the drug or class of drugs or may be limited to a specific species, indication, dosage form, route of administration, or combination of factors. 21 CFR 530.21 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.21)

FDA may prohibit the extra-label use of an animal or human drug in nonfood-producing animals if FDA determines that such extra-label use presents a risk to the public health. 21 CFR 530.30 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.30)

A list of drugs, families of drugs, and substances prohibited for extra-label use in animals appears in 21 CFR 530.41 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.41).

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Compounding Under AMDUCA

21 CFR 530.13 (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.13) provides specific conditions under which extralabel use from compounding of approved animal drugs or approved human drugs is permitted. The compounding must be in compliance with all relevant provisions of 21 CFR 530. The extralabel drug use regulation does not permit animal drug compounding from active pharmaceutical ingredients (bulk drugs).

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Additional Information

- Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 (http://uscode.house.gov/statutes/pl/103/396.pdf)
- 21 CFR 530.41 - Drugs prohibited for extralabel use in animals (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530#530.41)
- Extralabel Use and Antimicrobials (/animal-veterinary/antimicrobial-resistance/extralabel-use-and-antimicrobials)

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Appendix 20

The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians

As a practicing veterinarian, you've likely prescribed a drug for an extra-label use. What does that mean? What gives you the legal ability to do so? What conditions must you meet? By explaining FDA's requirements for extra-label drug use in animals, this article answers these questions and more.

In 1994, Congress enacted the Animal Medicinal Drug Use Clarification Act (AMDUCA) (/animal-veterinary/guidance-regulations/animal-medicinal-drug-use-clarification-act-1994-amduca), adding provisions to the Federal Food, Drug, and Cosmetic Act (FD&C Act) that give veterinarians the legal ability - with certain restrictions - to use approved human and animal drugs in an extra-label manner. This means, in some cases, you can use an approved drug in a way that isn't listed on the drug's labeling. Information about extra-label drug use is not on the approved label - it is a use that's "off of the label".

As a veterinarian who prescribes drugs in an extra-label manner, you need to understand FDA's requirements for extra-label drug use, as stated in the FD&C Act and FDA regulations. You should also educate your clients, particularly food animal producers, on these requirements.

Extra-Label Drug Use in Animals

Before Congress passed AMDUCA in 1994, federal law did not permit extra-label drug use in animals. The AMDUCA provisions (http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=5796afc35ca48b270d1bd427a77d60df&rgn=div5&view=text&node=21:6.0.1.1.16&idno=21) amended the FD&C Act to allow the use of approved human and animal drugs for extra-label uses in animals under specified conditions. The key points addressed in AMDUCA and the regulations established by FDA are:

- Valid Veterinarian-Client-Patient Relationship
- General Conditions for Extra-Label Drug Use
- Conditions for Extra-Label Drug Use in Food-Producing Animals
- Compounding
- Drugs Prohibited from Extra-Label Uses in Animals

We'll look at each point separately.

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Valid Veterinarian-Client-Patient Relationship

The AMDUCA provisions of the FD&C Act allow extra-label drug use only on the lawful order of a licensed veterinarian in the context of a valid veterinarian-client-patient relationship. FDA regulations in Title 21 of the Code of Federal Regulations Part 530.3 (21 CFR 530.3) define a valid veterinarian-client-patient relationship as one in which:

- you have assumed responsibility for making medical judgments about the health of an animal, or animals, and the need for medical treatment. In turn, the client (the owner or other animal caretaker) has agreed to follow your instructions;
- you have sufficient knowledge of the animal, or animals, to form at least a general or preliminary diagnosis of the medical condition; and
- you are readily available for follow-up in case of adverse reactions or treatment failure.

The definition states that such a relationship can exist only when you have recently seen and are personally acquainted with the keeping and care of the animal or animals by virtue of examination of the animal or animals and/or medically appropriate and timely visits to the premises (usually the case for food-producing animals), where the animals are kept.

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General Conditions for Extra-Label Drug Use

FDA's requirements for extra-label drug use in animals limits this use to situations where an animal's health is threatened or where the animal may suffer or die without treatment. This means that you cannot use a drug for a non-therapeutic purpose (i.e., production purpose) in an extra-label use manner. Also, the regulations limit extra-label use to situations where there is no approved new animal drug that is labeled for such use and that contains the same active ingredient in the dosage form and concentration that is required, except in situations where you find the approved new animal drug is clinically ineffective for its intended use.

Be aware that extra-label use is prohibited for conditionally approved and indexed animal drugs (/animal-veterinary/development-approval-process/minor-useminor-species). You cannot prescribe these drugs for any extra-label use.

Thorough recordkeeping is vital (/animal-veterinary/animal-health-literacy/adequate-drug-treatment-records-help-ensure-food-safety). You must maintain records that identify the treated animal or animals. For food-producing animals, this can be done on a group, herd, flock, or per-client basis. The records must include the:

- established name of the drug and its active ingredient, or if formulated from more than

one ingredient, the established name of each ingredient. Ordinarily, the established name of the drug is the name listed in the United States Pharmacopeia (USP) (http://www.usp.org/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) and is made up of the active ingredient, route of administration, and dosage form (for example, “fenbendazole oral suspension”);

- condition treated;
- animal species treated;
- dosage administered;
- treatment duration; and
- number of animals treated.
- For food-producing animals, the records must include the specified withdrawal, withholding, or discard time(s), if applicable, time for food products made from treated animals, such as meat, milk, and eggs.

You must keep these records for two years or as otherwise required by federal or state law, whichever is longer and permit FDA to, at all reasonable times, have access to, permit copying and verify such records.

Thorough labeling is critical. The labeling for a drug dispensed on your order for an extra-label use must state your name and address. If the drug is dispensed by a pharmacy on your order, the labeling must state your name and the name and address of the dispensing pharmacy. The labeling must also include information similar to what is required in the record:

- established name of the drug or, if formulated from more than one ingredient, the established name of each active ingredient. As mentioned above, the established name of the drug typically is the name listed in the USP and is made up of the active ingredient, route of administration, and dosage form (for example, “fenbendazole oral suspension”);
- directions for use, including: the class/species or identification of the animal or herd, flock, pen, lot, or other group of animals being treated; the dosage, frequency, and route of administration; and the duration of the therapy; and
- any cautionary statements (for example, “Not for use in veal calves”).
- For food-producing animals, the drug labeling must also include your specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food which might be derived from the treated animal or animals.

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Conditions for Extra-Label Drug Use in Food-Producing Animals

If you're a food animal veterinarian, you should be aware of the additional requirements for extra-label drug use in food-producing animals (https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530/subpart-C?toc=1). Before prescribing or dispensing any approved human or animal drug for an extra-label use in food-producing animals, you must:

- carefully diagnose and evaluate the condition for which the drug is to be used;
- institute procedures to ensure the identity of the treated animal or animals is carefully maintained;
- establish a substantially extended withdrawal period supported by appropriate scientific information. You may get this information from such sources as scientific literature, academia, or the Food Animal Residue Avoidance Databank (FARAD) (http://www.farad.org/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer); and
- take measures to assure withdrawal periods are met and no illegal drug residues occur in the treated animal or animals.

If you want to use a drug approved for people or a drug approved only for companion animals in food-producing animals, you must have:

- an appropriate medical rationale doing so, and
- scientific information on the safety of the drug in food products for people. If you do not have scientific information on the safety of the drug in food products for people, then you must take appropriate measures to assure the animal and its food products will not enter the human food supply.

Remember, you may not prescribe an approved human drug for food-producing animals if there's an animal drug approved for food-producing animals that you can prescribe instead.

The FD&C Act doesn't allow the extra-label use of any drug in animal feed. However, for some minor species (/animal-veterinary/animal-health-literacy/lions-and-tigers-and-bears-omums), you may determine that the extra-label use of a drug in animal feed is needed to prevent suffering and death in these animals. (Minor species are all animals that aren't one of the seven major species: cattle, horses, swine, chickens, turkeys, dogs, and cats.) Please refer to FDA's Compliance Policy Guide (/regulatory-information/search-fda-guidance-documents/cpg-sec-615115-extralabel-use-medicated-feeds-minor-species), which describes FDA's current thinking on the extra-label use of over-the-counter and Veterinary Feed Directive medicated feeds for minor species.

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Compounding

FDA's extralabel use regulations also address the compounding of animal drugs from an approved animal or human drug. This compounding is permitted under specific circumstances listed in 21 CFR 530.13(b). Animal drugs compounded from already approved animal and human drugs are considered an extra-label use and, as such, as long as the regulations in part 530 are met, would not result in the compounded drug being considered "unsafe" and therefore adulterated under the FD&C Act. However, FDA's extralabel use regulations specifically state that, "[n]othing in this part shall be construed as permitting compounding from bulk drugs." Thus, compounding animal drug from bulk drug substances results in an unapproved animal drug.

For more information about FDA's policy regarding animal drugs compounded from bulk drug substances, see "Guidance for Industry #256, Compounding Animal Drugs from Bulk Drug Substances (/regulatory-information/search-fda-guidance-documents/cvm-gfi-256-compounding-animal-drugs-bulk-drug-substances)." More information may also be found at Animal Drug Compounding (/animal-veterinary/unapproved-animal-drugs/animal-drug-compounding).

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Drugs Prohibited from Extra-Label Uses in Animals

Under certain circumstances, FDA can prohibit extra-label uses of certain drugs in animals. The following drugs (both human and animal), families of drugs, and substances are prohibited from extra-label uses in all food-producing animals:

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol (DES)
- Dimetridazole
- Ipronidazole and other nitroimidazoles
- Furazolidone and nitrofurazone
- Sulfonamide drugs in lactating dairy cattle, except for the approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine
- Fluoroquinolones
- Glycopeptides

- Phenylbutazone in female dairy cattle 20 months of age or older
- Cephalosporins (not including cephapirin) in cattle, swine, chickens, or turkeys:
    - For disease prevention purposes;
    - At unapproved doses, frequencies, durations, or routes of administration; or
    - If the drug is not approved for that species and production class.

The following drugs, or classes of drugs, that are approved for treating or preventing influenza A are prohibited from extra-label uses in chickens, turkeys, and ducks:

- Adamantane
- Neuraminidase inhibitors

The above list can be found in Section 530.41 of Title 21 of the Code of Federal Regulations (https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=5796afc35ca48b270d1bd427a77d60df&rgn=div5&view=text&node=21:6.0.1.1.16&idno=21%20-%2021:6.0.1.1.16.5.1.2) (Drugs prohibited for extra-label use in animals). Currently, no approved drugs are prohibited from extra-label uses in companion animals.

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Conclusion

The Animal Medicinal Drug Use Clarification Act of 1994 added provisions to the Federal Food, Drug, and Cosmetic Act authorizing the extra-label use of approved human and animal drugs in animals under certain conditions. You can ensure proper extra-label use by complying with FDA's requirements and by understanding what's allowed and what's not under the law.

For more information, please call FDA's Center for Veterinary Medicine at 240-402-7002, or email AskCVM@fda.hhs.gov (mailto:AskCVM@fda.hhs.gov).

Relevant Guidance Documents

- Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals (/regulatory-information/search-fda-guidance-documents/cvm-gfi-209-judicious-use-medically-important-antimicrobial-drugs-food-producing-animals)
- Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use

Conditions with GFI #209 (/regulatory-information/search-fda-guidance-documents/cvm-gfi-213-new-animal-drugs-and-new-animal-drug-combination-products-administered-or-medicated-feed)

- Guidance for Industry #256: Compounding Animal Drugs from Bulk Drug Substances (/regulatory-information/search-fda-guidance-documents/cvm-gfi-256-compounding-animal-drugs-bulk-drug-substances)

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Appendix 21

Government of Canada / Gouvernement du Canada

CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.311-2020 Corrigendum No. 1, March 2021 Organic production systems-Permitted substances lists

Supersedes CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.311-2015

International Classification for Standards (ICS) 67.040 / 67.120.30

Published by the Canadian General Standards Board

About the standard

This is a National Standard of Canada for organic food. The standard is written with specialized technical terms and is not considered plain language.

Substance name(s)	Origin and usage
Protein feeds	Shall be from organic sources.
Seaweed meal	
Vitamins	Permitted for enrichment or fortification. Vitamin formulants that comply with Canadian regulations are accepted. Vitamins not compliant to 5.1.2 of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.311 are permitted.

Table 5.3—Health care products and production aids

Substance name(s)	Origin and usage
Acetylsalicylic acid	Aspirin.
Acids	Ascorbic, acetic, propionic, citric, formic and lactic acids and vinegar. Permitted for all uses such as treatment of water and bedding.
Activated charcoal	Shall be of plant origin.
Alcohol, ethyl (ethanol)	Permitted as a disinfectant and sanitizer.

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Substance name(s)	Origin and usage
Alcohol, isopropyl	Permitted as a disinfectant.
Antibiotics	See 6.6 of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310, for conditions pertaining to antibiotic use in livestock. See Table 5.3 Antibiotics, oxytetracycline.
Antibiotics, oxytetracycline	For emergency use for bees. The equipment shall be destroyed, in accordance with 7.1.15.7 of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310; treated bees do not need to be destroyed if they are taken out of organic production.
Anti-inflammatories	Non-steroid anti-inflammatories such as ketoprofen. Preference shall be given to alternative products, such as those listed in Table 5.3, Botanical compounds; and Homeopathy and biotherapies. To reduce inflammation. See 6.6.4 c) 2) of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310.
Biologics	

Appendix 21

Substance name(s)	Origin and usage
Botanical compounds	Botanical preparations, such as atropine, butorphanol and other medicines from herbaceous plants shall be used according to label specifications. Substances containing petroleum-derived formulants, such as propylene glycol, shall not be fed to livestock.
Calcium borogluconate	For milk fever. No withdrawal period required.
Chlorhexidine	For surgical procedures conducted by a veterinarian. To be used as a post-milking teat dip when alternative germicidal agents and physical barriers have lost their effectiveness. See Table 5.3 Teat dips and udder wash.
Colostral whey	Probiotic.
Colostrum	Shall be organic if commercially available.
Copper sulphate	As an essential nutrient (source of copper and sulphur) and for topical use (foot baths).
Diatomaceous earth	For use in control of external parasites and as a preventative practice for control of internal parasites. For internal use, diatomaceous earth shall be food grade (non-calcined).

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Substance name(s)	Origin and usage
Electrolytes	Including, but not limited to: CMPK (Calcium, Magnesium, Phosphorus, Potassium), calcium propionate and calcium sulphate. Shall not contain antibiotics. Orally or by injection.
Formic acid	For apicultural use, to control parasitic mites. This substance may be used after the last honey harvest of the season and shall be discontinued 30 days before the addition of honey supers.
Formulants (inerts, excipients)	Shall be used in conjunction with substances listed in Table 5.3. Formulants are not subject to 1.4 or 1.5 of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310 or 5.1.2 of this standard.
Glucose	
Glycerol (glycerine, glycerin)	Shall be from organic sources if commercially available. Shall be from vegetable oil or animal fat. Shall be produced using fermentation or by hydrolysis.
Homeopathy and biotherapies	

Appendix 21

Substance name(s)	Origin and usage
Honey	Shall be organic.
Hydrated lime (calcium hydroxide)	Shall not be used to deodorize animal wastes.
Hydrogen peroxide	Pharmaceutical grade hydrogen peroxide is permitted for external use (disinfectant). Food-grade hydrogen peroxide is permitted for internal use (for example, added to livestock drinking water).
Iodine	If used as a topical disinfectant: permitted iodine sources include potassium iodide and elemental iodine. If used as a cleaning agent: non-elemental iodine shall be used; iodine shall not exceed 5% solution by volume (example: iodophors). Use shall be followed by a hot-water rinse.
Iron products	May be supplied by ferric phosphate, ferric pyrophosphate, ferrous lactate, ferrous sulphate, iron carbonate, iron gluconate, iron oxide, iron phosphate, iron sulphate or reduced iron.
Lanolin	For external use only, such as udder balm (ointment).

Appendix 21

Substance name(s)	Origin and usage
Local anesthetics	Such as lidocaine. Use of pharmaceutical local anesthetics shall be followed by withdrawal periods of 90 days for livestock intended for slaughter, and seven days for dairy animals. Preference shall be given to alternatives, such as clove oil, listed in Table 5.3 Botanical compounds; Homeopathy and biotherapies.
Magnesium sulphate	Mined sources. A source of magnesium and sulphur.
Mineral oil	For external use.
Minerals, trace minerals, elements	Non-synthetic chelated or sulphated minerals. Examples include oyster shell, calcium chloride and magnesium oxide. Synthetic nutrient minerals may be used if non-synthetic sources are not commercially available. Minerals from any source are permitted for medical use.
Microorganisms and yeasts	If organic sources of yeast are not commercially available, non-organic yeast sources derived from living yeast, including yeast autolysate, shall be used.
Oxalic acid	For mite control in honeybee colonies.

Appendix 21

Substance name(s)	Origin and usage
Oxytocin	For post-parturition therapeutic use. Meat from treated animals will not lose its organic status. See 6.6.10 d) of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310, for criteria pertaining to the mandatory withdrawal period.
Paraffin	Shall be food-grade. For use in hives.
Parasiticides and anti-microbials	Shall respect requirements set out in 6.6 of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310 with regard to the use of internal parasiticides.
Physical teat seals	All sources are permitted. Shall be free from antibiotics. For post-lactation use. Shall be completely removed prior to nursing or milking. Shall be prescribed and administered under veterinary supervision.
Plant oils	To control external parasites.
Prebiotics	From organic sources if commercially available.

Substance name(s)	Origin and usage
Probiotics	Probiotics may be administered orally, as dietary supplements, via pharmaceutical preparations in the form of capsules, tablets, alginate gels, or dry powder.
Propylene glycol	May only be used as an ingredient in foot baths.
Sedatives	Such as xylazine.
Selenium products	Derived from sodium selenate or sodium selenite. May be used to address documented deficiencies in the stock, soils or feed supplies. See Table 5.3 Minerals, trace minerals, elements.
Sodium hydroxide	For use in dehorning paste.
Sulphur	For control of external parasites.
Teat dips and udder wash	Substances, such as alcohol, iodine, hydrogen peroxide, chlorine dioxide and ozone, can be used as disinfectants for a pre- or post-teat dip or udder wash if they are registered for this use by Canada's *Food and Drug Regulations*. Chlorhexidine can be used as a post-milking teat dip if alternative germicidal agents and physical barriers have lost their effectiveness. See Table 5.3 Chlorhexidine.

Appendix 21

Substance name(s)	Origin and usage
Thymol	See Table 5.3 Botanical compounds for thymol derived from botanical sources. Thymol that is not derived from botanical sources may only be used in foot baths.
Vaccines	Vaccines may be used in prevention of diseases. If vaccines compliant to 5.1.2 of this standard are not commercially available, or are ineffective, vaccines not compliant to 5.1.2 are permitted.
Vitamins	Vitamin formulants that comply with Canadian regulations are accepted. Vitamins not compliant to 5.1.2 of this standard are permitted. Orally, topically or by injection.

6 Permitted substances lists for preparation

6.1 Classification

6.1.1 Processing substances are classified according to the following uses and applications:

a. Food additives (see definition in clause 3 of CAN/CGSB (National Standard of Canada/Canadian General Standards Board)-32.310)
b. Other ingredients not considered to be food additives
c. Processing aids (see definition in clause 3 of CAN/CGSB (National

Appendix 22

Technical Rules for Organic Production

MAF Standard OP3, Appendix Two

Ministry of Agriculture and Forestry
Te Manatū Ahuwhenua, Ngāherehere

BIOSECURITY NEW ZEALAND

NEW ZEALAND FOOD SAFETY AUTHORITY

Version 7.1

June 2011

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Disclaimer

Every effort has been made to ensure the information in this report is accurate.

MAF does not accept any responsibility or liability whatsoever for any error of fact, omission, interpretation or opinion that may be present, however it may have occurred.

Requests for further copies should be directed to:

Publication Adviser

MAF Information Bureau

P O Box 2526

WELLINGTON

Telephone: 0800 00 83 33

Facsimile: 04-894 0300

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These figures shall be calculated annually as a percentage of the dry matter of feed from agricultural origin.

The maximum percentage of conventional feed authorised for both herbivores and non-herbivores in the daily ration is 25% calculated as a percentage of the dry matter.

The operator shall keep documentary evidence of the need for the use of this provision.

6.4.11 When forage production is lost MAF can authorise the use of conventional feeds for a limited period and in relation to a specific area. This exception may be used as a result of adverse climatic conditions or other exceptional conditions.

The operator shall keep documentary evidence of use of this exception.

6.4.12 Roughage, fresh or dried fodder, or silage must be added to the daily ration for pigs and poultry.

6.4.13 Only products listed in Tables 3.4.5 and 3.6.1, respectively, can be used as additives and processing aids in silage

6.4.14 Conventional feed materials of agricultural origin can be used for animal feeding only if listed in Table 3.1, subject to the quantitative restrictions imposed in this Section 6, and only if they are produced or prepared without the use of chemical solvents

6.4.15 Feed materials from animal origin (whether conventional or organically produced) can only be used if listed in Table 3.2, and subject to the quantitative restrictions imposed in this Section 6.

6.4.16 In order to satisfy nutritional requirements of animals, only products listed in Table 3.3, Table 3.4.1 and Table 3.4.2 can be used for animal feeding

6.4.17 Only products listed in Table 3.4.3, Table 3.4.4, Table 3.4.5, Table 3.4.6, Table 3.4.7, Table 3.5 and Table 3.6 can be used in animal feeding for the purposes indicated in respect to the above mentioned categories. Antibiotics, coccidiostatics, medicinal substances, growth promoters or any other substance intended to stimulate growth or production shall not be used in organic animal feeding.

6.4.18 Feeds, feed materials, compound feeds, feed additives, processing aids for feeds and certain products used in animal nutrition must not have been produced with the use of genetically modified organisms or products derived from GMOs.

6.5 Disease prevention and veterinary treatment

6.5.1 Operators must ensure that animals are treated in accordance with all provisions of New Zealand animal welfare and veterinary medicines legislation. Only veterinary medicinal products that are authorised for the specified uses under the Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM Act), Hazardous Substances and New Organisms Act 1996 (HSNO Act) or are exempt are to be used.

6.5.2 Disease prevention in organic animal production is based on the following principles:

a. the selection of appropriate breeds or strains of animals as detailed in Section 6.3;

b. the application of animal husbandry practices appropriate to the requirements of each species, encouraging strong resistance to disease and the prevention of infections;

c. the use of high quality feed, together with regular exercise and access to grazing, having the effect of encouraging the natural immunological defence of the animals;

d. ensuring an appropriate density of animals, thus avoiding overstocking and any resulting animal health problems.

e. adequate and appropriate housing maintained in hygienic conditions

6.5.3 The principles set out in 6.5.2 should limit animal health problems so that they can be controlled mainly by prevention.

6.5.4 If, despite all of the above preventive measures, an animal becomes sick or injured, it must be treated immediately, if necessary in isolation, and in suitable housing.

6.5.5 The use of veterinary medicinal products in organic farming shall comply with the following principles:

a. Phytotherapeutic (e.g. plant extracts (excluding antibiotics), essences, etc.), homeopathic products (e.g. plant, animal or mineral substances) and trace elements and products listed in Table 3.3, Table 3.4.1 and Table 3.4.2 shall be used in preference to chemically-synthesised allopathic veterinary medicinal products or antibiotics, provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended;

b. If the use of these products is not effective in combating illness or injury, and treatment is essential to avoid suffering or distress to the animals, chemically-synthesised allopathic veterinary medicinal products or antibiotics may be used under the responsibility of a veterinarian.

6.5.6 The use of chemically-synthesised allopathic veterinary medicinal products or antibiotics for preventive treatments is not permitted in animals or products for which official organic assurances are sought.

6.5.7 In addition to the above principles, the following rules shall apply:

a. the use of substances to promote growth or production, (including antibiotics, coccidiostatics and other artificial aids for growth promotion purposes) and the use of hormones or similar substances to control reproduction (e.g. induction or synchronisation of oestrus), or for other purposes, is not permitted in animals or products for which official organic assurances are sought. Nevertheless, hormones may be administered to an individual animal, as a form of therapeutic veterinary treatment;

b. mandatory veterinary treatments to animals, or treatments to buildings, equipment and facilities including the use of immunological veterinary medicinal products when a disease risk has been recognised as present in a specific area in which the production unit is located, are authorised.

6.5.8 Whenever veterinary medicinal products are to be used the following information is to be declared to the TPA before official organic assurances are sought for the animals or animal products:

- type of product (including the active ingredient(s)) must be clearly recorded
- details of the diagnosis;
- the dosage;
- the method of administration;
- the duration of the treatment, and
- the legal withdrawal period.

Animals treated must be clearly identified, individually in the case of large animals; individually or by batch, in the case of poultry and small animals. Existing animal identification forms, vendor declarations or the like may be used.

6.5.9 The withdrawal period between the last administration of an allopathic veterinary medicinal product to an animal under normal conditions of use, and the production of organic products from such animals, is to be twice the legal withdrawal period or, in a case in which this period is not specified, 48 hours.

6.5.10 If animals receive more than three courses of treatment with chemically-synthesised allopathic veterinary medicinal products or antibiotics within one year, they are not eligible for official organic assurances. Products derived from them are also not eligible. This does not apply to mandatory vaccinations, treatments for parasites or any compulsory eradication schemes. Animals whose productive lifecycle is less than one year may not receive more than one such course of treatment. Animals which do receive more than the allowed treatments must undergo the conversion periods in Section 6.2.3.

The operator shall keep records of documented evidence of the occurrence of such circumstances for the TPA.

6.6 Husbandry practices

6.6.1 In principle, the reproduction of organically reared animals should be based on natural methods. Nevertheless artificial insemination is permitted. Other forms of artificial or assisted reproduction (for example embryo transfers) are not permitted.

6.6.2 In principle, operations such as attaching elastic bands to the tails of sheep, tail-docking, cutting of teeth, trimming of beaks and dehorning are not to be systematically carried out on animals in organic production. These operations (e.g. dehorning in young animals) may however, be authorised by the TPA, for reasons of safety or where normal New Zealand animal welfare or good

REGULATION (EU) 2018/848 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 30 May 2018

on organic production and labelling of organic products and repealing Council Regulation (EC) No 834/2007

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 43(2) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee (1),

Having regard to the opinion of the Committee of the Regions (2),

Acting in accordance with the ordinary legislative procedure (3),

Whereas:

(1) Organic production is an overall system of farm management and food production that combines best environmental and climate action practices, a high level of biodiversity, the preservation of natural resources and the application of high animal welfare standards and high production standards in line with the demand of a growing number of consumers for products produced using natural substances and processes. Organic production thus plays a dual societal role, where, on the one hand, it provides for a specific market responding to consumer demand for organic products and, on the other hand, it delivers publicly available goods that contribute to the protection of the environment and animal welfare, as well as to rural development.

(2) The observance of high standards for health, the environment and animal welfare in the production of organic products is intrinsic to the high quality of those products. As underlined in the communication of the Commission of 28 May 2009 on agricultural product quality policy, organic production forms part of the Union's agricultural product quality schemes, together with geographical indications and traditional specialities guaranteed in accordance with Regulation (EU) No 1151/2012 of the European Parliament and of the Council (4) and products of the outermost regions of the Union in accordance with Regulation (EU) No 228/2013 of the European Parliament and of the Council (5). In this sense, organic production pursues the same objectives within the common agricultural policy ('CAP'), which are inherent to all the agricultural product quality schemes of the Union.

ANNEX II

Part II: Livestock production rules

1.5. Health care

1.5.2. Veterinary treatment

1.5.2.1. Where animals become sick or injured despite preventive measures to ensure animal health, they shall be treated immediately.

1.5.2.2. Disease shall be treated immediately to avoid suffering of the animal. Chemically synthesised allopathic veterinary medicinal products, including antibiotics, may be used where necessary, under strict conditions and under the responsibility of a veterinarian, when the use of phytotherapeutic, homeopathic and other products is inappropriate. In particular, restrictions with respect to courses of treatment and withdrawal periods shall be defined.

Ordinance on Organic Farming and the Labelling of Organically Produced Products and Foodstuffs[1]

(Organic Farming Ordinance)

of 22 September 1997 (Status as of 1 September 2023)

Chapter 2 Requirements for Organic Production

Section 4 Livestock Production

Art. 16*d*[95] Animal health

[1] Disease prevention must be based on the following principles:

a. selection of suitable breeds or strains;

b. application of animal husbandry practices appropriate to the requirements of each species, encouraging strong resistance to disease and the prevention of infections;

c. the use of high-quality feed, together with regular exercise (pasture, outdoor run, outdoor climate area) to encourage the natural immunological defence of livestock;

d. ensuring an appropriate density of livestock, thus avoiding overstocking and any resulting animal health problems.

[2] If an animal becomes sick or injured, it must be treated immediately, if necessary in isolation, and in suitable housing.

[3] The use of veterinary medicinal products in organic stockfarming shall comply with the following principles:

a.

Phytotherapeutic products (e.g. plant extracts, excluding antibiotics, or plant essences), homeopathic products (e.g. plant, animal and mineral substances) and trace elements and products laid down by the Department for this purpose shall be used in preference to chemically-synthesised allopathic veterinary medicinal products or antibiotics, provided that their therapeutic effect is shown to be effective for the species of animal and the condition for which the treatment is intended.

b.

If the use of the products listed in letter a should not prove to be effective in combating illness or injury, but treatment is essential to prevent suffering or distress to the animal, chemically-synthesised allopathic veterinary medicinal products or antibiotics may be used under the responsibility of a veterinarian.

c.[96]

The use of coccidiostatics and the use of hormones or similar substances to control reproduction (e.g. induction or synchronisation of oestrus), or for other purposes, is not permitted. Nevertheless, hormones may be administered to an individual animal as a form of therapeutic veterinary treatment.

d.

The use of chemically-synthesised allopathic veterinary medicinal products or antibiotics for preventive treatments is not permitted.

[4] The type of product (including an indication of the active pharmacological substances involved) together with details of the diagnosis, the method of administration, the duration of the treatment and the prescribed withdrawal period must be recorded clearly and indelibly in writing in the treatment book.

[5] Livestock treated must be clearly identified as such at all times – individually in the case of large animals, individually or as a group, in the case of poultry or small animals.

[6] Vaccination and worming is permitted where there is an existing animal health risk.

[7] ...[97]

[8] The withdrawal period between the last administration of a chemically-synthesised allopathic veterinary medicinal product under normal conditions of use, and the production of organically produced foodstuffs from such animals must be twice the legal withdrawal period. This does not apply to the use of products to dry up cows with udder problems.

[9] With the exception of vaccinations, treatments for parasites, anaesthetic agents, pain relief treatments and treatments as part of state livestock epidemic programmes, where an animal or group of animals receives more than three courses of treatments with chemically-synthesised

allopathic veterinary medicinal products or antibiotics within one year (or more than one course of treatment if their production lifecycle is less than one year), the livestock concerned, or produce derived from them, shall not be sold as being produced in accordance with this Ordinance, and the livestock must undergo the conversion periods laid down in Article 16*f* paragraph 2.[98]

有機畜産物の日本農林規格
Japanese Agricultural Standards for Organic Livestock Products
有機畜産物の日本農林規格（平成十七年十月二十七日農林水産省告示第千六百八号）
Japanese Agricultural Standards for Organic Livestock Products (Public Notice of the Ministry of Agriculture, Forestry and Fisheries No. 1608 of October 27, 2005)
農林物資の規格化及び品質表示の適正化に関する法律（昭和二十五年法律第百七十五号）第七条第一項の規定に基づき、有機畜産物の日本農林規格を次のように定め、同法第十条第一項の規定に基づき公示する。
Pursuant to the provisions of Article 7, paragraph (1) of the Act on Standardization and Proper Quality Labeling of Agricultural and Forestry Products (Act No. 175 of 1950), the Japanese Agricultural Standards for organic livestock products are established as follows, and public notice is given pursuant to the provisions of Article 10, paragraph (1) of the same Act.

第４条　有機畜産物の飼養及び生産の方法についての基準は、次のとおりとする。
Article 4 The criteria for raising and production methods of organic livestock products are as follows:

健康管理
5. Health management

１　疾病予防を目的として、病気に対する抵抗力の強化及び感染予防が図られるよう家畜又は家きんの種類に応じた適切な飼養管理を行うこと。
(A) For the purpose of disease prevention, appropriate raising management is to be conducted according to the type of livestock or poultry so as to strengthen their resistance to diseases and prevent infection.

２　家畜又は家きんが傷病に罹患した場合、必要に応じて隔離し、迅速に治療すること。この場合において、家畜又は家きんが不必要に苦しむことのないよう、治療や処置を行うこと。
(B) In the case that livestock or poultry suffer from any injury or disease, they are to be isolated as necessary and treated promptly. In such cases, treatment and care is to be provided so that the livestock or poultry does not suffer unnecessarily.

３　特定の疾病若しくは健康上の問題が発生し、若しくは発生する可能性があって他に適当な治療方法若しくは管理方法がない場合又は法令（法律の規定に基づく命令及び処分を含む。以下同じ。）で義務付けられている場合を除き、動物用医薬品を使用しないこととし、動物用医薬品を使用する場合にあっては、要診察医薬品又は抗生物質以外の動物用医薬品を使用すること。
(C) Do not use veterinary medicinal products unless a specific disease or health problem has occurred or is likely to occur and no other appropriate treatment or control method is available, or unless required by laws and regulations (including orders and dispositions based on the provisions of laws; the same applies hereinafter). In the case where veterinary medicinal products are used, veterinary medicinal products other than medicines requiring medical examination or antibiotics are to be used.

４　家畜又は家きんへのビタミン、ミネラル、動物用生物学的製剤又は駆虫薬以外の動物用医薬品の使用は、治療目的に限ること。
(D) The use of vitamins, minerals, biological preparations for animal use or veterinary medicinal products other than parasiticides in livestock or poultry is to be for therapeutic purposes only.

５　３の基準にかかわらず、要診察医薬品又は抗生物質以外の動物用医薬品を用いた治療が効果的でない場合には、要診察医薬品又は抗生物質を使用することができる。ただし、次のいずれかに該当する場合は、それぞれ（１）又は（２）に掲げる期間、要診察医薬品又は抗生物質を使用することができない。
(E) Notwithstanding the criteria in (C) above, if treatment with veterinary medicinal products other than medicinal products requiring medical examination or antibiotics is not effective, medicinal products requiring medical examination or antibiotics may be used. However, in the case of any of the following, the medicinal products requiring medical examination or antibiotics may not be used for the period described in (1) or (2), respectively.

（１）　動物用医薬品の使用の規制に関する省令（昭和５５年農林水産省令第４２号）別表第１及び別表第２の医薬品の欄に掲げるものを使用する場合　それぞれ、当該医薬品の種類に応じてこれらの表の使用対象動物の欄に掲げる動物の種類に応じ、これらの表の使用禁止期間の欄に掲げる期間の２倍の期間
(1) In the case of the use of any of the medicinal products listed in the column of medicinal products in Appended Table 1 and Appended Table 2 of the Ministerial Order Concerning the Regulations on the Use of Veterinary Medicinal Products (Order of the Ministry of Agriculture, Forestry and Fisheries No. 42 of 1980): A period twice as long as the period listed in the column of "Prohibited period of use" in these tables according to each category of animals listed in the column of "Animals subject to use" in these tables in accordance with the category of relevant medicinal products.

（２）　（１）に掲げる医薬品以外の医薬品を使用する場合　と殺、搾乳若しくは採卵する前４８時間又は医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律第１４条第１項、第１４条第９項、第１４条の４及び第１４条の６に基づく医薬品等の承認、承認事項の変更、再審査及び再評価の際に定められる休薬期間（最後に投薬されてからと殺、搾乳若しくは採卵するまでの期間をいう。）の２倍のいずれか長い期間
(2) In the case of using medicinal products other than those listed in (1) above: A period of 48 hours prior to slaughtering, milking or egg collecting, or a period that is twice as long as the withholding period of drug (meaning the period from the last medication to the time of slaughtering, milking or egg collecting) specified in the approval, modification of approved matters, reexamination or reevaluation of pharmaceuticals, etc., based on Article 14, paragraph (1), Article 14, paragraph (9), Article 14-4 and Article 14-6 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, whichever is longer.

６　飼料以外の成長又は生産の促進を目的とした物質を給与しないこと。
(F) No substance intended to promote growth or production other than feed is to be fed.

Appendix 26

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature.

They're often used to relieve symptoms of:

- headaches (Link: www.nhs.uk/conditions/headaches/)
- painful periods (Link: www.nhs.uk/conditions/period-pain/)
- sprains and strains (Link: www.nhs.uk/conditions/sprains-and-strains/)
- colds (Link: www.nhs.uk/conditions/common-cold/) and flu (Link: www.nhs.uk/conditions/flu/)
- coronavirus (COVID-19) (Link: www.nhs.uk/conditions/coronavirus-covid-19/)
- conditions such as arthritis (Link: www.nhs.uk/conditions/arthritis/) that can cause long-term pain

Although NSAIDs are commonly used, they're not suitable for everyone and can sometimes cause side effects.

This information is a general overview of NSAIDs.

For information about a specific medicine, you can look up your medicine (Link: www.nhs.uk/medicines/) in the Medicines A to Z.

Types of NSAIDs

NSAIDs are available as tablets, capsules, suppositories (capsules inserted into the bottom), creams, gels and injections.

Some can be bought over the counter from pharmacies, while others need a prescription.

The main types of NSAIDs include:

- ibuprofen (Link: www.nhs.uk/medicines/ibuprofen-for-adults/)
- naproxen (Link: www.nhs.uk/medicines/naproxen/)

- diclofenac (Link: www.nhs.uk/medicines/diclofenac/)
- celecoxib
- mefenamic acid
- etoricoxib
- indomethacin
- aspirin for pain relief (Link: www.nhs.uk/medicines/aspirin-for-pain-relief/) (low-dose aspirin is not normally considered to be an NSAID)

NSAIDs may be sold or prescribed under these names or a brand name.

They're all similarly effective, although you may find a particular one works best for you.

Who can take NSAIDs

Most people can take NSAIDs, but some people need to be careful about taking them.

It's a good idea to ask a pharmacist or doctor for advice before taking an NSAID if you:

- are over 65 years of age
- are pregnant or trying for a baby
- are breastfeeding
- have asthma (Link: www.nhs.uk/conditions/asthma/)
- have had an allergic reaction (Link: www.nhs.uk/conditions/allergies/symptoms/) to NSAIDs in the past
- have had stomach ulcers (Link: www.nhs.uk/conditions/stomach-ulcer/) in the past
- have any problems with your heart, liver, kidneys, blood pressure, circulation or bowels
- are taking other medicines
- are looking for medicine for a child under 16 (do not give any medicine that contains aspirin to children under 16)

NSAIDs might not necessarily need to be avoided in these cases, but they should only be used on the advice of a healthcare professional as there may be a higher risk of side effects.

If NSAIDs are not suitable, your pharmacist or doctor may suggest alternatives to NSAIDs, such as paracetamol (Link: www.nhs.uk/medicines/paracetamol-for-adults/).

Side effects of NSAIDs

Like all medicines, there's a risk of side effects from NSAIDs.

These tend to be more common if you're taking high doses for a long time, or you're elderly or in poor general health.

Appendix 26

Over-the-counter NSAIDs generally have fewer side effects than stronger prescription medicines.

Possible side effects of NSAIDs include:

- indigestion (Link: www.nhs.uk/conditions/indigestion/) – including stomach aches (Link: www.nhs.uk/conditions/stomach-ache/), feeling sick and diarrhoea (Link: www.nhs.uk/conditions/diarrhoea/)
- stomach ulcers (Link: www.nhs.uk/conditions/stomach-ulcer/) – these can cause internal bleeding and anaemia (Link: www.nhs.uk/conditions/iron-deficiency-anaemia/); extra medicine to protect your stomach may be prescribed to help reduce this risk
- headaches (Link: www.nhs.uk/conditions/headaches/)
- drowsiness
- dizziness (Link: www.nhs.uk/conditions/dizziness/)
- allergic reactions
- in rare cases, problems with your liver, kidneys or heart and circulation, such as heart failure (Link: www.nhs.uk/conditions/heart-failure/), heart attacks (Link: www.nhs.uk/conditions/heart-attack/) and strokes (Link: www.nhs.uk/conditions/stroke/)

If you're bothered by side effects, stop taking your medicine and tell your doctor.

Interactions with other medicines

Some NSAIDs can react unpredictably with other medicines.

This can affect how well either medicine works and increase the risk of side effects.

It's particularly important to get medical advice before taking an NSAID if you're already taking:

- another NSAID
- low-dose aspirin (Link: www.nhs.uk/medicines/low-dose-aspirin/) or warfarin (Link: www.nhs.uk/medicines/warfarin/) – medicines used to prevent blood clots (Link: www.nhs.uk/conditions/blood-clots/)
- ciclosporin – a medicine used to treat autoimmune conditions, such as arthritis (Link: www.nhs.uk/conditions/arthritis/) or ulcerative colitis (Link: www.nhs.uk/conditions/ulcerative-colitis/)
- diuretics – medicines sometimes used to treat high blood pressure (Link: www.nhs.uk/conditions/high-blood-pressure-hypertension/)
- lithium – a medicine used to treat mental health problems, including bipolar disorder (Link: www.nhs.uk/conditions/bipolar-disorder/) and severe depression (Link: www.nhs.uk/conditions/clinical-depression/)
- methotrexate – a medicine used to treat inflammatory conditions such as rheumatoid arthritis (Link: www.nhs.uk/conditions/rheumatoid-arthritis/)
- a type of antidepressant medicine (Link: www.nhs.uk/conditions/antidepressants/) called a selective serotonin reuptake inhibitor (SSRI) (Link: www.nhs.uk/conditions/ssri-

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antidepressants/) – examples of SSRIs are citalopram (Link: www.nhs.uk/medicines/citalopram/) and fluoxetine (Prozac) (Link: www.nhs.uk/medicines/fluoxetine-prozac/)

If you're not sure whether a medicine you're taking is safe to take at the same time as an NSAID, check the leaflet that comes with it, or ask a pharmacist or doctor for advice.

Food and alcohol

The leaflet that comes with your medicine should say whether you need to avoid any particular foods or drinks. Ask your pharmacist or doctor if you're not sure.

For information about a specific medicine, check the product information about medicines on the GOV.UK website (Link: https://www.gov.uk/guidance/find-product-information-about-medicines).

Generally, you do not need to avoid any specific foods while taking NSAIDs.

Tablets or capsules should normally be swallowed whole, without chewing, and taken with water or food to stop them upsetting your stomach.

It's usually safe to drink alcohol while taking NSAIDs, but drinking alcohol excessively may irritate your stomach.

Overdoses of NSAIDs

Taking too much of an NSAID can be dangerous. This is known as taking an overdose.

Contact your GP or NHS 111 (Link: www.nhs.uk/using-the-nhs/nhs-services/urgent-and-emergency-care/nhs-111/) for advice immediately if you take too much of your medicine.

Call 999 for an ambulance immediately if you or someone else experiences serious effects of an overdose, such as fits (seizures), breathing difficulties, or loss of consciousness.

Alternatives to NSAIDs

As NSAIDs can cause troublesome side effects, alternatives are often recommended first.

The main alternative for pain relief is paracetamol (Link: www.nhs.uk/medicines/paracetamol-for-adults/), which is available over the counter and is safe for most people to take.

NSAID creams and gels that you rub into your skin may be worth trying first if you have muscle or joint pain (Link: www.nhs.uk/conditions/joint-pain/) in a particular part of your body, as they tend to have fewer side effects than tablets or capsules.

Your doctor may also be able to recommend different medicines and therapies depending on the health problem you have.

For example, physiotherapy (Link: www.nhs.uk/conditions/physiotherapy/) may help some people with muscle or joint pain.

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Page last reviewed: 07 October 2022
Next review due: 07 October 2025

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RETURN TO PET POISON CONTROL HOME PAGE

If you have any reason to suspect your pet has ingested something toxic, please contact your veterinarian or one of the other resources listed:
- ASPCA Animal Poison Control Center 24-hour hotline at (888) 426-4435
- Pet Poison Helpline® 24-hour animal poison control service at (855) 764-7661

Meloxicam

Generic name: Meloxicam
Brand Name: Metacam

While meloxicam, an NSAID, is approved for use to treat pain and inflammation in some animals, chronic use may cause toxicity. It is important to discontinue the use of prescribed NSAIDs when your veterinarian tells you to do so. Toxicity can also occur if your pet consumes more medication than prescribed.

It is important to note that other veterinary NSAIDs (such as deracoxib, carprofen, ketoprofen, firocoxib, and tepoxalin) carry similar toxicity risks.

Signs and symptoms of toxicity:
vomiting, abdominal pain, melena (black, tarry stool), diarrhea. These signs may occur within an hour of ingestion. Weakness, involuntary muscle movements, and seizures may also occur and these are signs of severe toxicity.

More severe toxicity (GI perforation or renal failure) may not occur until 48-72 hours after ingestion. Signs of kidney damage include increased thirst, increased urination, loss of appetite or refusal to eat, fatigue, and vomiting.

Toxic consumption:
Doses greater than 5 times the therapeutic dose can result in toxicity.

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In cats, acute or chronic doses of any medication may cause toxicity.

In dogs, signs of toxicity can be seen with doses up to 5 times the therapeutic dose (0.1-0.5 mg/kg).

Long-term use, even at therapeutic doses, can result in clinical signs of toxicity.

Dogs: Meloxicam Toxic Consumption					
X-Small Yorkie, Chihuahua	**Small** Pug, Boston Terrier, Poodle	**Medium** Beagle, Scottish Terrier	**Large** Boxer, Cocker Spaniel	**X-Large** Labrador & Golden Retrievers, German Shepherd	**XX-Large** Great Dane, St. Bernard
1 – 10 lbs. (0.45 – 4.6 kg)	11 – 25 lbs. (5 – 11.4 kg)	26 – 40 lbs. (11.8 – 18.2 kg)	41 – 70 lbs. (18.6 – 31.8 kg)	71 – 90 lbs. (32.3 – 40.9 kg)	91 – 110 lbs. (41.4 – 50 kg)
					
> 0.2 mg	> 2.5 mg	> 5.5 mg	> 9 mg	> 16 mg	> 20.5 mg

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Related Projects

Baclofen

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Appendix 28

Meloxicam: A toxicology overview

Published: June 1996 4, 105–123 (1996)

InflammoPharmacology

Aims and scope

Submit manuscript

H. A. Lehmann, M. Baumeister, L. Lützen & J. Wiegleb

Abstract

Meloxicam is a new potent non-steroidal anti-inflammatory drug (NSAID), which in animal tests exhibits potential antiarthritic action and has a wider spectrum of anti-inflammatory activity than currently available NSAIDs. Toxicological testing of meloxicam in animals suggests that acute oral overdosage is unlikely to cause severe toxicity in man. Compared with other NSAIDs, meloxicam has a relatively weak effect on gastric acid secretion and on ulceration in the rat stomach. Whereas most NSAIDs can cause parenchymal kidney damage in animals at low plasma levels and over relatively short periods, meloxicam only induces such damage in the rat over the longer term. Meloxicam preferentially inhibits cyclooxygenase-2 (COX-2), rather than cyclooxygenase-1 (COX-1), which may explain its

good gastric and renal tolerability. Meloxicam was chondroneutral in long-term studies in rats and mice. It was significantly less phototoxic in vitro than diclofenac, ketoprofen and naproxen, but similar to piroxicam and tenoxicam. There was no evidence of mutagenic, clastogenic, teratogenic or tumorigenic activity on immunogenic potential.

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Author information

Authors and Affiliations

Dr Karl Thomae GmbH, Birkendorfer Strasse 65, D-88397, Biberach an der Riss, Germany

H. A. Lehmann, M. Baumeister, L. Lützen & J. Wiegleb

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Safety Data Sheet
acc. to OSHA HCS

Printing date 09/27/2023 Revision date 09/27/2023

*
1 Identification

· **Product identifier**

· **Trade name: Meloxicam**
· **Synonym**
4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-1,1-dioxide-2H-1,2-benzothiazine-3-carboxamide
UH-AC 62XX

· **Article number:** 14906
· **CAS Number:**
71125-38-7
· **EC number:**
615-253-8
· **Application of the substance / the mixture**
This product is for research use - Not for human or veterinary diagnostic or therapeutic use.

· **Details of the supplier of the safety data sheet**
· **Manufacturer/Supplier:**
Cayman Chemical Co.
1180 E. Ellsworth Rd.
Ann Arbor, MI 48108
USA

· **Information department:** Product safety department
· **Emergency telephone number:**
During normal opening times: +1 (734) 971-3335
US/CANADA: 800-424-9300
Outside US/CANADA: 703-741-5970

*
2 Hazard(s) identification

· **Classification of the substance or mixture**


GHS06 Skull and crossbones

Acute Toxicity - Oral 3 H301 Toxic if swallowed.


GHS08 Health hazard

Toxic to Reproduction 1A H360 May damage fertility or the unborn child.

Aquatic Chronic 3 H412 Harmful to aquatic life with long lasting effects.

· **Label elements**
· **GHS label elements**
The substance is classified and labeled according to the Globally Harmonized System (GHS).

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Trade name: Meloxicam

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· **Hazard pictograms**

GHS06 GHS08

· **Signal word** Danger
· **Hazard statements**
H301 Toxic if swallowed.
H360 May damage fertility or the unborn child.
H412 Harmful to aquatic life with long lasting effects.
· **Precautionary statements**
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P264 Wash thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P273 Avoid release to the environment.
P280 Wear protective gloves/protective clothing/eye protection/face protection.
P301+P310 If swallowed: Immediately call a poison center/doctor.
P321 Specific treatment (see on this label).
P330 Rinse mouth.
P308+P313 IF exposed or concerned: Get medical advice/attention.
P405 Store locked up.
P501 Dispose of contents/container in accordance with local/regional/national/international regulations.
· **Classification system:**
· **NFPA ratings (scale 0 - 4)**

Health = 2
Fire = 0
Reactivity = 0

· **HMIS-ratings (scale 0 - 4)**

Health = *2
Fire = 0
Reactivity = 0

· **Other hazards**
· **Results of PBT and vPvB assessment**
· **PBT:** Not applicable.
· **vPvB:** Not applicable.

3 Composition/information on ingredients

· **Chemical characterization: Substances**
· **CAS No. Description**
71125-38-7 Meloxicam
· **Identification number(s)**
· **EC number:** 615-253-8

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4 First-aid measures

· **Description of first aid measures**
· **General information:**
Immediately remove any clothing soiled by the product.
In case of irregular breathing or respiratory arrest provide artificial respiration.
· **After inhalation:** In case of unconsciousness place patient stably in side position for transportation.
· **After skin contact:** Immediately wash with water and soap and rinse thoroughly.
· **After eye contact:** Rinse opened eye for several minutes under running water. Then consult a doctor.
· **After swallowing:** Do not induce vomiting; immediately call for medical help.
· **Information for doctor:**
· **Most important symptoms and effects, both acute and delayed**
No further relevant information available.
· **Indication of any immediate medical attention and special treatment needed**
No further relevant information available.

5 Fire-fighting measures

· **Extinguishing media**
· **Suitable extinguishing agents:**
Use fire fighting measures that suit the environment.
A solid water stream may be inefficient.
· **Special hazards arising from the substance or mixture** No further relevant information available.
· **Advice for firefighters**
· **Protective equipment:** No special measures required.

6 Accidental release measures

· **Personal precautions, protective equipment and emergency procedures** Not required.
· **Environmental precautions:**
Inform respective authorities in case of seepage into water course or sewage system.
Do not allow to enter sewers/ surface or ground water.
· **Methods and material for containment and cleaning up:**
Dispose contaminated material as waste according to section 13.
· **Reference to other sections**
See Section 7 for information on safe handling.
See Section 8 for information on personal protection equipment.
See Section 13 for disposal information.
· **Protective Action Criteria for Chemicals**
· **PAC-1:** Substance is not listed.
· **PAC-2:** Substance is not listed.
· **PAC-3:** Substance is not listed.

*

7 Handling and storage

· **Handling:**
· **Precautions for safe handling** Thorough dedusting.
· **Information about protection against explosions and fires:** No special measures required.

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· **Conditions for safe storage, including any incompatibilities**
Keep container tightly closed.
Store in accordance with information listed on the product insert.
· **Storage:** Store in accordance with information listed on the product insert.
· **Requirements to be met by storerooms and receptacles:** No special requirements.
· **Information about storage in one common storage facility:** Not required.
· **Further information about storage conditions:** None.
· **Specific end use(s)** No further relevant information available.

8 Exposure controls/personal protection

· **Additional information about design of technical systems:** No further data; see section 7.

· **Control parameters**
· **Components with limit values that require monitoring at the workplace:** Not required.
· **Additional information:** The lists that were valid during the creation were used as basis.

· **Exposure controls**
· **Personal protective equipment:**
· **General protective and hygienic measures:**
Keep away from foodstuffs, beverages and feed.
Immediately remove all soiled and contaminated clothing.
Wash hands before breaks and at the end of work.
· **Breathing equipment:** Not required.
· **Protection of hands:**
The glove material has to be impermeable and resistant to the product/ the substance/ the preparation.
Due to missing tests no recommendation to the glove material can be given for the product/ the preparation/ the chemical mixture.
Selection of the glove material on consideration of the penetration times, rates of diffusion and the degradation
· **Material of gloves**
The selection of the suitable gloves does not only depend on the material, but also on further marks of quality and varies from manufacturer to manufacturer.
· **Penetration time of glove material**
The exact break through time has to be found out by the manufacturer of the protective gloves and has to be observed.
· **Eye protection:** Not required.

9 Physical and chemical properties

· **Information on basic physical and chemical properties**	
· **General Information**	
· **Appearance:**	
Form:	Crystalline
Color:	Not determined.
· **Odor:**	Characteristic
· **Structural Formula**	C14H13N3O4S2
· **Molecular Weight**	351.4 g/mol
· **Odor threshold:**	Not determined.
· **pH-value:**	Not applicable.

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Trade name: Meloxicam

(Contd. from page 4)

· **Change in condition**	
Melting point/Melting range:	Undetermined.
Boiling point/Boiling range:	Undetermined.
· **Flash point:**	Not applicable.
· **Flammability (solid, gaseous):**	Product is not flammable.
· **Decomposition temperature:**	Not determined.
· **Ignition temperature:**	Not determined.
· **Danger of explosion:**	Product does not present an explosion hazard.
· **Explosion limits:**	
Lower:	Not determined.
Upper:	Not determined.
· **Vapor pressure:**	Not applicable.
· **Density:**	Not determined.
· **Relative density**	Not determined.
· **Vapor density**	Not applicable.
· **Evaporation rate**	Not applicable.
· **Solubility in / Miscibility with**	
Water:	Not determined.
· **Partition coefficient (n-octanol/water):**	Not determined.
· **Viscosity:**	
Dynamic:	Not applicable.
Kinematic:	Not applicable.
SOLUBILITY	~0.5 mg/ml in a 1:1 solution of DMSO:PBS (pH 7.2); ~20 mg/ml in DMSO & DMF
· **Other information**	No further relevant information available.

10 Stability and reactivity

· **Reactivity** No further relevant information available.
· **Chemical stability**
· **Thermal decomposition / conditions to be avoided:**
No decomposition if used according to specifications.
· **Possibility of hazardous reactions** No dangerous reactions known.
· **Conditions to avoid** No further relevant information available.
· **Incompatible materials:** strong oxidizing agents
· **Hazardous decomposition products:** carbon oxides, hydrogen sulfide, nitrogen oxides

11 Toxicological information

· **RTECS Number** DL0702000

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Trade name: Meloxicam

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· **Information on toxicological effects**
· **Acute toxicity:**

· **LD/LC50 values that are relevant for classification:**		
Oral	TDLO	1 mg/kg (rat)
	Subcutaneous TDLO	0.5 mg/kg (mouse)
	Intraperitoneal TDLO	1.25 mg/kg (rat)

· **Primary irritant effect:**
· **on the skin:** No irritant effect.
· **on the eye:** No irritating effect.
· **Sensitization:** No sensitizing effects known.
· **Additional toxicological information:**

· **Carcinogenic categories**
· **IARC (International Agency for Research on Cancer)** Substance is not listed.
· **NTP (National Toxicology Program)** Substance is not listed.
· **OSHA-Ca (Occupational Safety & Health Administration)** Substance is not listed.

12 Ecological information

· **Toxicity**
· **Aquatic toxicity:** No further relevant information available.
· **Persistence and degradability** No further relevant information available.
· **Behavior in environmental systems:**
· **Bioaccumulative potential** No further relevant information available.
· **Mobility in soil** No further relevant information available.
· **Ecotoxical effects:**
· **Remark:** Harmful to fish
· **Additional ecological information:**
· **General notes:**
Water hazard class 2 (Assessment by list): hazardous for water
Do not allow product to reach ground water, water course or sewage system.
Danger to drinking water if even small quantities leak into the ground.
Harmful to aquatic organisms
· **Results of PBT and vPvB assessment**
· **PBT:** Not applicable.
· **vPvB:** Not applicable.
· **Other adverse effects** No further relevant information available.

13 Disposal considerations

· **Waste treatment methods**
· **Recommendation:**
Must not be disposed of together with household garbage. Do not allow product to reach sewage system.

· **Uncleaned packagings:**
· **Recommendation:** Disposal must be made according to official regulations.

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*

14 Transport information

· **UN-Number**	
· **DOT, IMDG, IATA**	UN2811
· **UN proper shipping name**	
· **DOT**	Toxic solids, organic, n.o.s. (Meloxicam)
· **IMDG**	TOXIC SOLID, ORGANIC, N.O.S. (Meloxicam)
· **IATA**	Toxic solid, organic, n.o.s. (Meloxicam)
· **Transport hazard class(es)**	
· **DOT**	

· **Class**	6.1 Toxic substances
· **Label**	6.1
· **IMDG, IATA**	

· **Class**	6.1 Toxic substances
· **Label**	6.1
· **Packing group**	
· **DOT, IMDG, IATA**	III
· **Environmental hazards:**	Not applicable.
· **Special precautions for user**	Warning: Toxic substances
· **Hazard identification number (Kemler code):**	60
· **EMS Number:**	F-A,S-A
· **Stowage Category**	A
· **Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code**	Not applicable.
· **Transport/Additional information:**	
· **DOT**	
· **Quantity limitations**	On passenger aircraft/rail: 100 kg On cargo aircraft only: 200 kg
· **IMDG**	
· **Limited quantities (LQ)**	5 kg
· **Excepted quantities (EQ)**	Code: E1 Maximum net quantity per inner packaging: 30 g Maximum net quantity per outer packaging: 1000 g
· **IATA**	
· **Remarks:**	When sold in quantities of less than or equal to 1 mL, or 1 g, with an Excepted Quantity Code of E1, E2, E4, or E5, this item meets the De Minimis Quantities exemption, per IATA 2.6.10. Therefore packaging does not have to be labeled as

(Contd. on page 8)

Appendix 8

Safety Data Sheet
acc. to OSHA HCS

Printing date 09/27/2023 Revision date 09/27/2023

Trade name: Meloxicam

(Contd. from page 7)

·	Dangerous Goods/Excepted Quantity.
· **UN "Model Regulation":**	UN 2811 TOXIC SOLID, ORGANIC, N.O.S. (MELOXICAM), 6.1, III

15 Regulatory information

· **Safety, health and environmental regulations/legislation specific for the substance or mixture**
No further relevant information available.
· **Sara**
· **Section 355 (extremely hazardous substances):** Substance is not listed.
· **Section 313 (Specific toxic chemical listings):** Substance is not listed.
· **TSCA (Toxic Substances Control Act):** Substance is not listed.
· **Hazardous Air Pollutants** Substance is not listed.
· **Proposition 65**
· **Chemicals known to cause cancer:** Substance is not listed.
· **Chemicals known to cause reproductive toxicity for females:** Substance is not listed.
· **Chemicals known to cause reproductive toxicity for males:** Substance is not listed.
· **Chemicals known to cause developmental toxicity:** Substance is not listed.

· **Carcinogenic categories**
· **EPA (Environmental Protection Agency)** Substance is not listed.
· **TLV (Threshold Limit Value)** Substance is not listed.
· **NIOSH-Ca (National Institute for Occupational Safety and Health)** Substance is not listed.
· **Chemical safety assessment:** A Chemical Safety Assessment has not been carried out.

16 Other information

All chemicals may pose unknown hazards and should be used with caution. This SDS applies only to the material as packaged. If this product is combined with other materials, deteriorates, or becomes contaminated, it may pose hazards not mentioned in this SDS. Cayman Chemical Company assumes no responsibility for incidental or consequential damages, including lost profits, arising from the use of these data. It shall be the user's responsibility to develop proper methods of handling and personal protection based on the actual conditions of use. While this SDS is based on technical data judged to be reliable, Cayman Chemical Company assumes no responsibility for the completeness or accuracy of the information contained herein.

· **Department issuing SDS:** Environment protection department.
· **Contact:** -
· **Date of preparation / last revision** 09/27/2023
· **Abbreviations and acronyms:**
IMDG: International Maritime Code for Dangerous Goods
DOT: US Department of Transportation
IATA: International Air Transport Association
EINECS: European Inventory of Existing Commercial Chemical Substances
CAS: Chemical Abstracts Service (division of the American Chemical Society)
NFPA: National Fire Protection Association (USA)
HMIS: Hazardous Materials Identification System (USA)
LC50: Lethal concentration, 50 percent
LD50: Lethal dose, 50 percent
PBT: Persistent, Bioaccumulative and Toxic
vPvB: very Persistent and very Bioaccumulative
NIOSH: National Institute for Occupational Safety
OSHA: Occupational Safety & Health
TLV: Threshold Limit Value
PEL: Permissible Exposure Limit
REL: Recommended Exposure Limit

(Contd. on page 9)

Safety Data Sheet
acc. to OSHA HCS

Appendix 8

Printing date 09/27/2023 Revision date 09/27/2023

Trade name: Meloxicam

(Contd. from page 8)

Acute Toxicity - Oral 3: Acute toxicity – Category 3
Toxic to Reproduction 1A: Reproductive toxicity – Category 1A
Aquatic Chronic 3: Hazardous to the aquatic environment - long-term aquatic hazard – Category 3

· *** Data compared to the previous version altered.**

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Graduate Student Literature Review: Role of pain mitigation on the welfare of dairy calves undergoing disbudding*

Cassandra N. Reedman,[1]† Todd F. Duffield,[1] Trevor J. DeVries,[2] Kerry D. Lissemore,[1] and Charlotte B. Winder[1]‡
[1]Department of Population Medicine, University of Guelph, Guelph, ON, N1G 2W1 Canada
[2]Department of Animal Biosciences, University of Guelph, Guelph, ON, N1G 2W1 Canada

ABSTRACT

This review synthesizes research findings on the pain and welfare of dairy calves undergoing disbudding procedures. We describe disbudding practices in North America as well as the use and perceptions of pain control for these procedures. Governing bodies across Canada and the United States, including each country's veterinary medical association and nationwide initiatives such as proAction and Farmers Assuring Responsible Management (FARM), recommend or require the use of a local anesthetic, a nonsteroidal anti-inflammatory drug (NSAID), and a sedative for disbudding procedures. Although the use of pain relief for disbudding has increased over the past decade or so, some in the dairy industry still do not believe that pain control for disbudding is necessary. As a painful procedure, disbudding has numerous welfare impacts on the calf both during and following the procedure that can be categorized under all 3 principles of animal welfare: natural living, biological functioning, and affective state. The use of pain control for disbudding; namely, a local anesthetic and NSAID, can improve welfare outcomes such as procedure-induced pain behavior, cortisol concentrations, mechanical nociceptive threshold, emotional states, and so on, compared with no pain control for the procedure. Although extensive research exists on pain control practices for disbudding, this review identified further gaps in knowledge and areas for future research. Mechanical nociceptive threshold can be evaluated around the disbudding wounds and is a reliable test in older calves; however, this outcome in very young calves after caustic paste disbudding has been reported to be inconclusive compared with that in older calves. As well, research evaluating xylazine sedation for disbudding has reported both potentially positive and negative results that are difficult to interpret or base suggestions on for the use of this drug. Finally, wounds caused by disbudding take a long time to heal (up to 13 wk) and have increased sensitivity for the entire healing process. Therefore, future research should aim to (1) determine accurate behavioral tests for calves under 1 wk of age undergoing disbudding to better understand their experience, (2) further attempt to understand the effects of xylazine sedation for disbudding and potential impacts of providing this medication, and (3) determine more ways to reduce the healing time and pain experienced by the calf after disbudding procedures.

Key words: dehorning, dairy, heifer, welfare

INTRODUCTION

Disbudding is a painful husbandry procedure commonly performed on dairy operations; when performed without the use of either anesthesia and analgesia (or both together), it has been identified as a risk factor for poor calf welfare (Calderón-Amor and Gallo, 2020). In the United States, 94% of responding dairy farms reported having dehorned animals (NAHMS, 2018) and in Canada, over 95% of responding producers reported that they disbud their calves (Winder et al., 2018a). Cattle are typically dehorned or disbudded because horned dairy cattle pose a risk of injury to people as well as to other animals (reviewed by Stock et al., 2013).

Disbudding is the removal of the horn-forming tissue before its attachment to the skull, whereas dehorning is the removal of the horn after this occurs, typically at 2 to 3 mo of age (CVMA, 2016). Disbudding is recommended over dehorning, because it is less invasive and less painful (Stafford and Mellor, 2005, 2011).

Horned dairy cattle demonstrate a higher proportion of agonistic behaviors without body contact (such as a cow retreating from the horned cow without any body contact necessary) as well as more aggressive behaviors compared with dehorned cattle (Lutz et al., 2019).

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†Corresponding author: creedman@uoguelph.ca
‡Advisor (winderc@uoguelph.ca).

Additionally, in beef cattle, one of the most prevalent causes of carcass wastage is bruising, and dehorned cattle require less feeding trough space than horned cattle (Stock et al., 2013). Although one of the natural uses of horns on cattle were for protective or defensive purposes, today's modern domesticated dairy cattle do not have the same need for such a tool (Stock et al., 2013). For these reasons, polled or disbudded cattle may be more desirable in production systems and can decrease the amount of aggressive behavior and injury observed among a group of animals.

DISBUDDING PRACTICES

Disbudding Methods

The 2 most commonly used methods for disbudding are cautery (or hot iron) and caustic paste disbudding, with cautery disbudding being the most common (NAHMS, 2018; Winder et al., 2018a). A 2015 survey of Canadian producers reported that 86% of respondents used cautery disbudding as their primary method and 9% used caustic paste (Winder et al., 2018a). Similarly, in the United States in 2014, 70% of respondents reported disbudding their calves with a cautery iron and 16% with caustic paste (NAHMS, 2018); however, there may be regional differences in the use of disbudding products, as a recent survey performed among Wisconsin producers reported that 61% of respondents use of caustic paste for disbudding (Saraceni et al., 2021). Animals above 3 mo of age typically require surgical amputation dehorning. In Canada and the United States, approximately 11% of producers use surgical amputation (gouge or scoop) to dehorn their calves (NAHMS, 2018; Winder et al., 2018a). A producer's decision to use one method over another may be based on the size of their dairy operation and their labor capacity. Cautery disbudding has been reported as the primary method used on dairy operations under 500 cows [74.2% of small operations (30–99 cows) and 71.7% of medium operations (100–499 cows)], whereas caustic paste is used on a higher percentage of large operations (500+ cows; 28.2%) compared with small operations (9.9%) (NAHMS, 2018).

Age at Disbudding

Caustic paste is generally used on younger calves compared with cautery disbudding (NAHMS, 2018; Winder et al., 2018a). The majority (73%) of Canadian producers that use caustic paste disbudding disbud their calves before 3 wk of age (Winder et al., 2018a), and the mean age for this same procedure in the United States is 2.3 wk (NAHMS, 2018). In contrast, the mean age for hot-iron disbudding in the United States is 7.1 wk (NAHMS, 2018), and in Canada most (67%) producers using hot-iron disbudding disbud their calves between 3 and 8 wk of age (Winder et al., 2018a).

Disbudding Recommendations and Requirements

Although there is no specific legislation on pain mitigation for disbudding in Canada or the United States, the Canadian Veterinary Medical Association (CVMA) supports the use of disbudding in cattle and recommends the appropriate use of anesthesia and analgesia to help control the pain from the procedure (CVMA, 2016). In the United States, the American Veterinary Medical Association (AVMA) also recommends a combination of sedation, anesthetics, and analgesics as best practice for disbudding dairy calves (AVMA, 2014). In 2017, the Dairy Farmers of Canada implemented a national, industry-led quality assurance program that requires producers to use both a local anesthetic and a nonsteroidal anti-inflammatory drug (**NSAID**) before disbudding of any method (DFC, 2017). Before this requirement, 66% of responding producers used a local anesthetic, 33% provided sedation, and only 25% of producers reported use of an NSAID for cautery disbudding procedures (Winder et al., 2018a). Similarly, in the United States, the National Milk Producers Federation in partnership with Dairy Management Inc. created the National Dairy Farmers Assuring Responsible Management (**FARM**) program to work with dairy farmers aiming to provide assurance to customers that the dairy industry is producing milk with integrity. Producers who participate in FARM have new expectations as of 2020 that require disbudding to occur before 8 wk of age, pain control to be used for disbudding, and for a veterinarian to be involved when creating a disbudding protocol (FARM, 2020). Disbudding before 8 wk of age was recently increased in status from a Continuous Improvement Plan to a Mandatory Action Plan through FARM. Although it is not a requirement for producers to participate in FARM, many milk processors do require it; therefore, 99% of the US milk supply is now covered under the FARM program (National Dairy Farm Program, 2020).

Disbudding Changes Over Time

The most common change in disbudding practices over time is the adoption of pain control methods (Winder et al., 2016). Two surveys were performed in 2004 and 2014 in Ontario, Canada, assessing practices for disbudding and dehorning dairy calves by veterinarians and producers (Misch et al., 2007; Winder et al., 2016). Of respondents to the more recent survey, 72% of

veterinarians and 63% of producers reported that they had altered their disbudding practices since the first survey (Winder et al., 2016). Both veterinarians and producers reported that the changes that they made involved adding local anesthetics, sedation, NSAIDs, or a combination thereof to their pain control protocol (Winder et al., 2016). It was also reported that 30% of producers who changed their disbudding practice also began providing these medications to calves at younger ages (Winder et al., 2016). When responding veterinarians were asked what influenced their change in pain control provision over time, the most highly cited reason was concern for welfare of the calf, with 75% of responding veterinarians selecting this as a concern (Winder et al., 2016).

Reasons for Pain Control Use

Although the use of pain relief for disbudding has increased over the past decade or so (Winder et al., 2016; Robles et al., 2021), there are still some in the dairy industry who do not believe that pain control for disbudding is necessary. Some producers and veterinarians in North America have reported the cost of pain relief as a reason they do not provide pain mitigation for disbudding (Hewson et al., 2007; Robbins et al., 2015; Robles et al., 2021). Calf age at the time of disbudding can also be a factor associated with whether a producer decides to use pain mitigation or not. Caustic paste is more commonly used on younger calves, and it has been reported that producers from Ontario, Canada, have higher odds of providing their calves with pain control (odds ratio = 6.0, 95% CI: >1.0, 35.7) when performing cautery compared with caustic paste disbudding (Winder et al., 2016). Producers in North America have also reported they felt disbudding at a younger age did not require pain relief, as they believed young calves were less sensitive to pain (Robbins et al., 2015); however, there is no evidence to support this belief.

Perception of Pain

Many producers perceive disbudding to be a painful procedure (Hoe and Ruegg, 2006) and are in favor of pain control use (Kling-Eveillard et al., 2015). However, many individuals do not believe that disbudding causes significant or long-term pain for the calf (Robbins et al., 2015). In a survey by Winder et al. (2016), both producers and veterinarians reported that they perceived surgical dehorning at 5 mo of age to be more painful than cautery disbudding at 2 mo of age, and cautery disbudding at 2 mo of age to be more painful than caustic paste disbudding at 2 d of age. Perception of pain caused by gouge dehorning at 5 mo of age had the least amount of variation in score across participants, whereas caustic paste disbudding at 2 d of age showed the greatest variation (Winder et al., 2016). These results suggest greater agreement among producers that gouge dehorning is considered a painful practice for calves, but less agreement on the pain caused by caustic paste disbudding. Although some producers may believe that caustic paste disbudding causes high levels of pain to the animal, others do not view this procedure to cause significant pain and potentially do not see it as a welfare concern compared with other disbudding procedures, such as cautery disbudding or gouge dehorning.

Literature Review Objectives

The welfare of animals can be understood in different ways. For the purposes of this literature review, we assessed the welfare of calves following disbudding procedures using the 3 quality of life concerns proposed by Fraser et al. (1997): natural living, biological functioning, and affective state. The most commonly evaluated ways that the pain caused by disbudding can affect the welfare of the calf can be effectively classified and interpreted under each of these 3 sections. The term "natural living" is determined by both the housing of the animal (i.e., the naturalness of their environment) and the animal's ability to live according to its "nature" or display its natural behaviors (Fraser et al., 1997). The biological functioning approach includes the assessment of disease, injury, nutrition, diet, and other potential interruptions to what would be considered the animal's normal functioning. Last, the affective state of the animal refers to its subjective state and ability to experience affective states such as suffering or pleasure, and it is an important part of the evaluation of their quality of life (Fraser et al., 1997). A recent literature review on welfare and disbudding in dairy calves focused on the effects of combining an NSAID and local anesthetic for only hot-iron disbudding in calves <3 mo of age (Herskin and Nielsen, 2018). However, the aim of this review is to contribute to the conversation on pain and welfare for disbudding and the need for research in these areas to reduce pain and improve the welfare of calves undergoing any form of disbudding with any method of pain control in North America.

NATURAL LIVING AND DISBUDDING

Social Behavior

In nature, in the past, calves would have lived in a social environment, but social housing is not com-

mon on modern dairy operations (Costa et al., 2016). In Canada, 21% of farms house calves using group-housing systems and 79% house calves individually (Medrano-Galarza et al., 2017). Calves reared in social isolation (an absence or low frequency of direct peer interaction for an extended period) have been reported to have deficient social skills and cognitive deficits and difficulty coping in novel situations (Costa et al., 2016) compared with their group-housed counterparts.

Even when provided with local anesthetic and an NSAID, calves disbudded using cautery are reported to seek physical and visual isolation in group housing for up to 3 d after disbudding more often than non-disbudded calves in the same group, suggesting that this procedure affects the natural social behavior of calves under current pain control (Gingerich et al., 2020).

Play Behavior

Certain behaviors can be motivated by both positive and negative affects, whereas behavior such as play in calves is most likely motivated by only one affect (positive; Fraser and Duncan, 1998). Play is a natural behavior for calves that increases in frequency when the basic needs of the animal are met; however, it can be affected by management practices on dairy operations (Jensen et al., 2015). Play behavior reduces when animals are exposed to negative stimuli and it serves as a self-rewarding behavior for calves (Mintline et al., 2013); therefore, it can be considered a potential indicator of positive welfare in animals (Held and Spinka, 2011; Ahloy-Dallaire et al., 2018). However, whether increased play behavior is indicative of optimal welfare or just neutral welfare in animals is controversial (Ahloy-Dallaire et al., 2018). For the purposes of disbudding literature, play is typically considered an indicator of positive welfare.

Providing a calf with pain control for cautery disbudding (a local anesthetic and an NSAID) can result in increased play compared with calves receiving less pain control for the procedure (Mintline et al., 2013). The provision of a xylazine sedative in conjunction with a local anesthetic and NSAID can result in reduced play behavior for 3 h after cautery disbudding but can also increase play behavior 24 h after disbudding (Reedman et al., 2021). These results were only recorded in the short term (3–24 h; Mintline et al., 2013; Reedman et al., 2021), and further research evaluating the longer-term pain effects from disbudding and their effect on the play behavior of calves would be beneficial for fully understanding the impact of this procedure on the welfare of the animal.

Standing and Lying Behavior

Many researchers have used the evaluation or disruption of lying behavior patterns as an indicator of pain in animals. The change in the proportion of time that an animal spends lying down as well as their frequency of moving from standing to lying positions and vice versa (restlessness) are considered good indicators of whether an animal is experiencing pain or discomfort (Molony and Kent, 1997). Stressful events such as disbudding, weaning, or illness have been reported to cause a change in the lying behavior of calves (Molony and Kent, 1997; Black et al., 2017; Sutherland et al., 2018a).

Calves have been reported to be more restless (frequent standing up and lying down) in the first 4 h after disbudding (Morisse et al., 1995) and to spend less time lying down from 180 min (Molony and Kent, 1997) up to 4 h (Sutherland et al., 2019) after a painful procedure. In the 48 h following disbudding procedures, calves have been reported to spend less time lying and have shorter lying bouts compared with before the procedure (Sutherland et al., 2018b). Few studies have focused on examining the lying behavior of calves over a longer period following disbudding.

Provision of NSAIDs and local anesthetics reduces these changes in behavior that occur with disbudding (Theurer et al., 2012; Sutherland et al., 2018b, 2019). More specifically, in the short term, the provision of a local anesthetic with or without an NSAID can result in increased lying times in the first hour after disbudding (Sutherland et al., 2018b), and administering an NSAID compared with no pain control can result in increased lying times for up to 4 d after cautery disbudding (Theurer et al., 2012).

Feeding Behavior

Following cautery disbudding procedures, disbudded calves have fewer unrewarded visits to an automated milk feeder compared with calves that were not disbudded; this difference was eliminated with provision of a local anesthetic and an NSAID (Sutherland et al., 2018a). Other researchers have also reported that following disbudding, feeding behavior (time spent eating feed and drinking milk) is reduced in calves (Graf and Senn, 1999), but providing a local anesthetic can eliminate this reaction to the procedure.

BIOLOGICAL FUNCTIONING AND DISBUDDING

Wound Healing

Cautery disbudding wounds may take anywhere from 3 to 13 wk to re-epithelialize (Huebner et al., 2017;

Adcock and Tucker, 2018; Adcock et al., 2019). During this healing process, wounds are painful for at least 3 wk, and the different tissue types present during the healing process are more sensitive than new epithelium (new tissue formed after disbudding wounds have healed) for up to 13 wk (Adcock and Tucker, 2018). Adcock and Tucker (2018) determined that it takes 9 to 13 wk for wounds to re-epithelialize; however, calves in that study were fed a restricted milk volume (<6 L/d; Adcock and Tucker, 2018). Calves given free access to milk will typically drink about 20% of their BW per day or approximately 10 to 12 L/d of milk (Khan et al., 2011). Feeding high levels of milk to young dairy calves has been associated with improved calf health and performance (Todd et al., 2017) as well as reduced healing times after cautery disbudding (Reedman et al., 2022).

Adcock et al. (2019) compared the effects of different disbudding irons on wound healing but did not detect any difference, prompting further research to explore other strategies to decrease healing time following this procedure. There are different types and brands of cautery irons and caustic paste as well as highly variable management routines (e.g., housing conditions, nutritional management, health management) among countries, regions, farms, and producers. Further research exploring some of these different attributes may help to inform optimal strategies for reducing healing time after disbudding.

Heart Rate, Respiratory Rate, and Eye Temperature

Disruptions to a calf's normal biological functioning by pain or stress can be quantified using changes to the autonomic nervous system such as heart rate and heart rate variability, respiratory rate, and eye temperature (Stewart et al., 2008). Evaluating these outcomes can help us in determining the effect of pain and disbudding on the calf's bodily functions. Heart rate is increased compared with baseline following cautery disbudding procedures (Stock et al., 2015) and compared with that of sham-disbudded calves (Heinrich et al., 2009). This heart rate increase is lessened with the use of a local anesthetic (Stewart et al., 2008) or an NSAID (Coetzee et al., 2012) or both medications together compared with less or no pain control (Heinrich et al., 2009). The use of a local anesthetic has also been shown to decrease respiratory rate following disbudding (Heinrich et al., 2009), as well as a local anesthetic with an NSAID (Winder et al., 2017). Providing calves with a local anesthetic for cautery disbudding results in a smaller effect on the change in eye temperature compared with no pain control (Stewart et al., 2008). Researchers have also detected no difference in heart rate up to 24 h after disbudding (Stock et al., 2015) or in heart and respiratory rate up to 95.5 h after disbudding (Stock et al., 2016) between groups of disbudded calves provided with an NSAID and a local anesthetic compared with those only provided with a local anesthetic.

Cortisol

In calves, cortisol has been used as an indicator of pain and stress following cautery disbudding (Black et al., 2017). After disbudding, cortisol concentrations rise rapidly in the first 15 to 30 min (Winder et al., 2018b); these concentrations also increase with stress from being handled and sham disbudded (Heinrich et al., 2009). Cortisol has anti-inflammatory effects (Hannibal and Bishop, 2014) and, following an increase in cortisol concentrations due to pain from disbudding when no pain control is provided, cortisol concentrations decrease to baseline values after 3 to 7 h, likely due to these anti-inflammatory effects (Winder et al., 2018b; Reedman et al., 2020).

Amputation dehorning has been reported to elicit a larger cortisol response than disbudding (Petrie et al., 1996), and it may take more than 8 h for these concentrations to return to baseline (McMeekan et al., 1998). Providing calves with a local anesthetic for disbudding procedures eliminates the acute cortisol peak normally observed in the first 30 min after the procedure (Graf and Senn, 1999; Morisse et al., 1995; Reedman et al., 2020); however, local anesthetics are only effective for 1 to 3 h after administration. Once the local anesthetic wears off, a delayed cortisol peak is observed, similar to that observed immediately after the procedure without a local anesthetic (Stilwell et al., 2009, 2012). Therefore, although a local anesthetic is effective at reducing the acute pain from the disbudding procedure for 1 to 3 h (Stafford et al., 2003), it does not eliminate all pain when used alone. Providing a calf with an NSAID alone does not eliminate the initial cortisol peak in the first 30 min after disbudding, but it does aid in decreasing cortisol concentrations sooner than if no pain control is given (Glynn et al., 2013; Stock et al., 2015; Reedman et al., 2020). When both a local anesthetic and NSAID are provided to the calf for disbudding, both the acute and delayed cortisol responses are eliminated (Stilwell et al., 2009; Winder et al., 2018b; Reedman et al., 2020). Although the local anesthetic is effective at eliminating acute pain (the first cortisol peak) for 1 to 3 h after disbudding, the NSAID works to prevent the delayed peak, which usually occurs 4 h after disbudding, through anti-inflammatory effects. In some cases, the cortisol response of calves provided with both medications does not differ from those of sham-disbudded control calves (Winder et al., 2018b). Assessing cortisol

concentrations is helpful for understanding the benefit of pain mitigation in improving the welfare of the calf.

Results in the literature on cortisol concentrations evaluating the efficacy of xylazine sedation for disbudding have been inconclusive. Xylazine can provide effective restraint for the disbudding procedure. Some researchers have reported that xylazine (especially when paired with a local anesthetic) can reduce (but not eliminate) the initial cortisol response after disbudding for 45 min (Caray et al., 2015) up to about 3 h (Stafford et al., 2003), whereas others have reported plasma cortisol concentrations to be greater in xylazine-sedated calves compared with calves that did not receive this medication (Stilwell et al., 2010). Some of these differences could be attributed to how cortisol was collected and evaluated (through salivary or plasma concentrations) or to a difference in study designs. However, there is very little research on the effects of xylazine sedation for disbudding and the literature suggests that cortisol may be an unreliable indicator of pain in xylazine-sedated calves (Stilwell et al., 2010), potentially due to the effects of xylazine on the calf, which include decreased arterial pressure and reduced tissue oxygenation (Campbell et al., 1979; Hodgson et al., 2002). Xylazine also does not have an anesthetic effect but provides conscious sedation by causing muscle relaxation and limits the ability of the animal to move or react to stimuli (Stilwell et al., 2010); thus, it has been reported that sedation alone does not control the pain of disbudding (Grøndahl-Nielsen et al., 1999; Stilwell et al., 2010). Further research examining the effects of xylazine sedation for disbudding would be beneficial in understanding the effect of providing this medication to calves.

Haptoglobin

Inflammation caused by procedures such as disbudding can result in increased haptoglobin concentrations over time (Allen et al., 2013; Glynn et al., 2013). The provision of a local anesthetic and an NSAID results in lowered haptoglobin concentrations (for up to 2–3 d) compared with calves provided with less or no pain control for disbudding procedures (Ballou et al., 2013; Erdogan et al., 2019; Reedman et al., 2020).

Growth

Researchers have reported improved ADG in calves that received analgesics for scoop dehorning procedures compared with controls (Glynn et al., 2013). Pain relief for disbudding has been reported by multiple researchers as a factor that contributes to improved growth rate and weight gain after disbudding (Glynn et al., 2013; Bates et al., 2015, 2016). Specifically, calves provided with an NSAID for disbudding had higher growth rates than calves not provided an NSAID (Bates et al., 2015), and calves that received a sedative and a local anesthetic for disbudding had higher growth rates than calves that received no pain control or an NSAID alone (Bates et al., 2016).

Although feeding behavior and milk intake have been reported to change in response to pain from disbudding, there are conflicting results in the literature on whether this pain (and the changes that it causes) affects the growth and weight gain of calves. Although some researchers have reported no detectable differences between cautery-disbudded and non-disbudded calves (Grøndahl-Nielsen et al., 1999), others have detected a decrease in these parameters after painful procedures such as cautery disbudding (Black et al., 2017). It would be beneficial to conduct a meta-analysis on this topic to help discern whether there is a true difference in growth and weight gain in calves after disbudding compared with non-disbudded calves and depending on pain control methods used.

Mechanical Nociceptive Threshold

A pressure force algometer or von Frey monofilaments can be used to assess the mechanical nociceptive threshold (**MNT**) of the wound area following cautery or caustic paste disbudding (Adcock and Tucker, 2018; Reedman et al., 2020). After disbudding procedures, MNT in disbudded calves is much lower than baseline values or MNT in sham-disbudded calves (Allen et al., 2013; Adcock and Tucker, 2018). Using this test, it has been reported that during the healing process (which can take up to 13 wk), every tissue type present during this time was more sensitive compared with newly epithelialized disbudding wounds (Adcock and Tucker, 2018). Researchers have reported that disbudding wounds are more sensitive after the procedure anywhere from 4 to 9 h (Frahm et al., 2020), 24 h (Stock et al., 2015; Frahm et al., 2020), 48 h (Stock et al., 2016), 3 wk (Adcock and Tucker 2018), and up to 105 d (Casoni et al., 2019) compared with their baseline values before the procedure or compared with values in sham-disbudded calves. Therefore, an increased response to the MNT test can persist for long periods following disbudding.

The provision of a locally applied anesthetic before disbudding can reduce short-term pain and sensitivity, as evidenced by higher MNT values from 1 to 3 h after the procedure (Glynn et al., 2013; Stock et al., 2015; Reedman et al., 2020). Pain mitigation such as NSAIDs (which provide longer-term relief than local anesthetics) given in addition to a local anesthetic can result in

higher MNT values for up to 4 to 6 h after the procedure (Stock et al., 2016; Winder et al., 2018b). However, not all studies comparing a local anesthetic alone to a local anesthetic plus an NSAID have detected a difference in MNT values (Winder et al., 2018b). Although NSAIDs serve a similar purpose, many different types of NSAID are used to control pain following disbudding procedures (e.g., meloxicam, carprofen, ketoprofen, firocoxib). A study by Stock et al. (2015) examined MNT in calves following disbudding given both a local anesthetic and firocoxib compared with a local anesthetic alone and did not detect any differences between the treatment groups. In contrast, a study by Stock et al. (2016) detected a tendency for calves treated with both a local anesthetic and carprofen to be less sensitive than a local anesthetic alone. Winder et al. (2018b) compared MNT values in calves provided both an NSAID and local anesthetic with calves provided a local anesthetic alone in a meta-analysis and found calves to be less sensitive 4 to 6 h after disbudding when provided with both medications.

Most research evaluating MNT around the horn buds of calves after disbudding have been conducted on calves older than 1 wk of age, and there is limited research evaluating MNT in calves younger than this. However, MNT results in 1- to 9-d-old calves after caustic paste disbudding differed from those in calves older than this (also disbudded using caustic paste), as no difference was detected in MNT values between 1- and 9-d-old calves disbudded with no pain control and sham-disbudded calves from 15 min to 300 h after disbudding (Karlen et al., 2019; Reedman et al., 2020). This illustrates a gap in the knowledge for evaluating pain from disbudding in young calves under 1 wk of age. The MNT tests in these young calves are inconclusive and show different results compared with calves over 1 wk of age. Further research in this novel area would be beneficial for understanding the overall pain experience of these very young calves, as it is common to disbud calves before they are 1 wk of age.

AFFECTIVE STATE AND DISBUDDING

Behavioral Indicators of Pain

Calves exhibit certain behavior patterns more frequently after disbudding with less pain control; these are considered behavioral indicators of pain and are indicative of a negative affective state. Examples include tail flicking, head shaking, ear flicking, and vocalizing. Calves show more head shaking, ear flicking, and head rubbing after cautery disbudding compared with sham-disbudded calves (Faulkner and Weary, 2000).

The provision of a local anesthetic for disbudding results in reduced tail flicking, head shaking, and ear flicking compared with calves with no anesthetic (Winder et al., 2018b). Following the duration of effect of a local anesthetic (approximately 1 to 3 h following administration), calves that received a local anesthetic displayed behavioral indicators of pain that were not different from those of calves that did not receive an anesthetic (Graf and Senn, 1999; Stilwell et al., 2009). These indicators are decreased to the level of a sham control calf for up to 24 h (study end) when both a local anesthetic and an NSAID are used (Winder et al., 2018b). However, recent work by Thomsen et al. (2021) reported that 42% of calves disbudded with a hot iron and provided with a local anesthetic showed at least 1 of 3 behaviors examined (getting up, kicking, or lifting head), suggesting inadequate local anesthesia. Differences in these results could be attributed to study design or local anesthetic type and application method.

Although there is evidence in the literature of an NSAID (in combination with a local anesthetic) reducing behavioral indicators of pain for up to 24 h, few studies have examined longer-term pain. One study evaluated the behavioral indicators of pain of calves 11 d after the cautery disbudding procedure and the effect of additional medication at this time (Adcock et al., 2020). Calves that received an additional injection of a local anesthetic 11 d later had reduced head shaking and ear flicking compared with calves that did not; this difference was no longer detectable after 1 h when the local anesthetic wore off (Adcock et al., 2020). These results aid in understanding the length of time that calves experience pain after the disbudding procedure. Further research evaluating the length of time over which calves display behavioral indicators of pain would be beneficial in understanding the potential benefits of additional pain medication and the full impact of the procedure on the long-term welfare of the calf.

Other Indicators of Affective State

Researchers can assess the emotional states or responses in calves by evaluating their cognitive changes through the assessment of cognitive bias (Neave et al., 2013; Lecorps et al., 2020) and potential signs of anhedonia (Lecorps et al., 2020). Neave et al. (2013) reported that calves are more likely to judge ambiguous cues as negative after disbudding than before the procedure, indicating that the calves were more pessimistic after the painful procedure. In further work, researchers began more thoroughly examining the emotional state of calves after disbudding through different methods such as examining potential signs of anhedonia following

disbudding (Lecorps et al., 2020) and calf perception of pain after disbudding (Adcock and Tucker, 2020). Calves have been reported to be more pessimistic after disbudding and to display signs that may be interpreted as anhedonia, either consuming less of a highly desirable sweet solution (Lecorps et al., 2020) or perceiving the value of a reward that they were conditioned to expect as lower compared with before the procedure (Lecorps et al., 2019). Alternatively, using risk aversion methods, Adcock and Tucker (2021) reported disbudded calves to accept more risk compared with control calves to suckle (for up to 3 wk after disbudding) possibly as a strategy to mitigate pain, suggesting that disbudding influences motivational states for weeks after the procedure. These changes in the emotional state of calves after disbudding were previously reported to continue anywhere from 5 (Lecorps et al., 2020) to 20 d (Adcock and Tucker, 2020) after the procedure.

Another way that animal welfare researchers have attempted to understand the experience of calves after disbudding is through conditioned place avoidance. These experimental paradigms can provide a strong basis for examining the affective component of pain through learned responses from the animal rather than relying on physiological and behavioral indicators. Ede et al. (2019) examined this paradigm in calves in response to post-procedural pain from hot-iron disbudding and following intramuscular, intranasal, and subcutaneous injections (Ede et al., 2018). These researchers reported that an NSAID (meloxicam) treatment (in conjunction with a local anesthetic) made hot-iron disbudding less aversive to calves in the 6 h after their procedure (Ede et al., 2019). It was also reported that intramuscular injections were found to be the most aversive, with calves injected intramuscularly exhibiting a longer latency to drink milk compared with the other treatment groups (Ede et al., 2018). These novel methods of exploring the affective state of calves after disbudding show great promise and should be explored further and used more frequently in research.

CONCLUSIONS

Disbudding is a common procedure in the dairy industry and has been well documented to be painful and a significant welfare concern. Pain mitigation can alleviate some of the negative pain-related outcomes associated with the procedure; however, some people still do not believe that pain control is necessary when disbudding calves. Although research on the welfare of calves after disbudding has mainly focused on evaluating outcomes relating to the health and biological functioning of the calf, researchers have begun to shift focus to better understand the affective state of the calves during and following this procedure. Newer research has identified long-term effects of disbudding on the affective and motivational states of calves, and on their biological functioning, including very long healing times (up to 13 wk). Future research should aim to (1) determine accurate behavioral tests to assess pain for calves less than a week of age undergoing disbudding, (2) further understand the effects of xylazine sedation for disbudding, and (3) determine more ways to reduce the healing time after disbudding procedures.

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ORCIDS

Cassandra N. Reedman https://orcid.org/0000-0003-3904-0993
Todd F. Duffield https://orcid.org/0000-0001-6035-4669
Trevor J. DeVries https://orcid.org/0000-0001-9364-2456
Kerry D. Lissemore https://orcid.org/0000-0003-2979-4708
Charlotte B. Winder https://orcid.org/0000-0002-7314-3657

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Effects of local anesthetic or systemic analgesia on pain associated with cautery disbudding in calves: A systematic review and meta-analysis

Charlotte B. Winder,*[1] Cynthia L. Miltenburg,* Jan M. Sargeant,*† Stephen J. LeBlanc,* Derek B. Haley,* Kerry D. Lissemore,* M. Ann Godkin,‡ and Todd F. Duffield*
*Department of Population Medicine, and
†Centre for Public Health and Zoonoses, University of Guelph, Ontario, N1G 2W1 Canada
‡Ontario Ministry of Agriculture, Food, and Rural Affairs, Elora, Ontario, N0B 1S0 Canada

ABSTRACT

Disbudding is a common management procedure performed on dairy farms and, when done without pain mitigation, is viewed as a key welfare issue. Use of pain control has increased in recent years, but full adoption of anesthesia and analgesia by veterinarians or dairy producers has not been achieved. This may in part be due to the lack of a consistent recommendations of treatment protocols between studies examining pain control methods for disbudding. The objective of this systematic review was to examine the effects of these pain control practices for the most common method of disbudding, cautery, on outcomes associated with disbudding pain in calves. The outcomes were plasma cortisol concentrations, pressure sensitivity of the horn bud area, and validated pain behaviors (ear flick, head shake, head rub, foot stamp, and vocalization). Intervention studies describing cautery disbudding in calves 12 wk of age or younger were eligible, provided they compared local anesthesia, nonsteroidal anti-inflammatory drug (NSAID), or local anesthesia and NSAID to 1 or more of local anesthesia, NSAID, or no pain control. The search strategy used the Agricola, Medline (via OvidSP), and Web of Science databases, as well as the Searchable Proceedings of Animal Conferences (S-PAC), ProQuest Dissertations and Theses Database, and Open Access Theses and Dissertations. Meta-analysis was performed for all outcomes measured at similar time points with more than 2 studies. Local anesthetic was associated with reduced plasma cortisol until 2 h postdisbudding; however, a rise in cortisol was observed in the meta-analysis of studies reporting at 4 h postdisbudding. Heterogeneity was present in several of the analyses for this comparison. The addition of NSAID to local anesthetic showed reduction in plasma cortisol at 4 h, and a reduction in pressure sensitivity and pain behaviors in some analyses between 3 and 6 h postdisbudding. Heterogeneity was present in some meta-analyses, including several using pain behavior outcomes. This may reflect the variation in measurement time periods for behavioral measures between studies, as well as differences among NSAID treatments. Overall, a protective effect of local anesthetic was seen for the acute pain of cautery disbudding, and the delayed rise in cortisol was mitigated by the addition of an NSAID, which also reduced other signs of pain, including pressure sensitivity and pain behaviors. Based on these findings, we recommend use of local anesthetic and an NSAID as best practices for pain mitigation for cautery disbudding of calves 12 wk of age or less. The magnitude and duration of the effect of NSAID treatment was not possible to deduce from the literature because wide variation existed between studies. We recommend consideration of more standardized outcome measurements, especially for pain behaviors. Adherence to reporting guidelines by authors would help ensure more transparent and complete information is available to end users.

Key words: systematic review, meta-analysis, disbudding, pain

INTRODUCTION

Pain control for the disbudding or dehorning of cattle is a key animal welfare issue in the dairy industry (Ventura et al., 2015). Although NSAID analgesia in addition to local anesthesia has generally been found to be beneficial, the lack of specific recommendations for analgesia protocols may reflect the variety examined in the literature. Full compliance has not been achieved by producers or veterinarians in North America with regard to the use of local anesthetic and a nonsteroidal anti-inflammatory drug (**NSAID**; Adams et al., 2015; Winder et al., 2016), which is the current recommendation of industry and veterinary groups regarding pain

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[1]Corresponding author: winderc@uoguelph.ca

control (Canadian Veterinary Medical Association, 2010; American Veterinary Medical Association, 2014; Dairy Farmers of Canada, 2015). Although arresting horn growth can be done by surgical amputation, cautery, or use of chemical methods, cautery disbudding remains the most commonly used method by dairy producers in North America, with 89, 70, and 77% reporting use in the United States; Ontario, Canada; and Quebec, Canada, respectively (Vasseur et al., 2010; Adams et al., 2015; Winder et al., 2016).

Part of the gap between primary research and application in the dairy industry may be driven by the lack of a consistent set of recommendations from primary research papers. Likewise, narrative reviews typically do not include evidence-based methods to identify, assess, and synthesize results; as a result, conclusions may suffer from bias. Conversely, properly conducted systematic reviews offer a more robust and transparent methodology to identify, evaluate, and summarize evidence on a given topic (Sargeant and O'Connor, 2014). Meta-analyses also allow for synthesis of overall effects as well as identification and exploration of causes of heterogeneity among studies, possibly identifying sources of variability that may be further examined or used to guide inferences of the robustness of the observed effects across different study designs or settings (Sargeant and O'Connor, 2014).

The objectives of our systematic review were to examine the effects of local anesthesia or NSAID analgesia on plasma cortisol, pressure sensitivity, and pain behaviors following cautery disbudding. If enough studies reported on a given outcome at a similar time point, meta-analysis was conducted. This review should serve as a stronger form of evidence for the effects of these practices than narrative reviews or the results of a single research study. Our review will identify gaps in this body of literature and the degree, or lack, of homogeneity among reported interventions and outcomes, which should serve to inform future research designs and study reporting. This manuscript was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement (Moher et al., 2010).

MATERIALS AND METHODS

Protocol and Registration

A review protocol was created a priori in accordance with PRISMA-P guidelines (Moher et al., 2015) and deposited with the University of Guelph Atrium on April 26, 2017 (http://hdl.handle.net/10214/10324) and is also available via Systematic Reviews for Animals and Food (http://www.syreaf.org/contact/). The protocol is included in Supplemental File S1 (https://doi.org/10/3168/jds.2017-14092).

Eligibility Criteria

Primary Study Design, Characteristics, and Populations. Primary experimental intervention studies available in English, including both randomized and nonrandomized clinical trials, were eligible for inclusion. Observational study designs were not eligible. Studies must have involved bovine calves 12 wk of age or less who underwent cautery disbudding with no concurrent painful procedures, defined as 1 or more of castration, branding, or any surgical procedure.

Intervention and Comparator Groups. Eligible studies must have included at least 2 of the following experimental groups: no pain control given, local anesthetic alone, NSAID alone, or local anesthetic and NSAID.

Outcome Measures. Many outcomes have been used in disbudding studies as indicators of pain. For inclusion in our systematic review, studies must have included 1 or more of the following outcomes, measured at 1 or more time points: plasma cortisol, pain behaviors (one or more of ear flick, head shake, head rub, tail swish, foot stamp, and vocalization; Faulkner and Weary, 2000; Heinrich et al., 2010), or sensitivity of the horn bud (e.g., measured by an algometer or von Frey monofilaments; Heinrich et al., 2010; Mintline et al., 2013). These outcomes were chosen based on consideration of their use in the literature.

Information Sources

Electronic searches were completed using Agricola (https://search-proquest-com.subzero.lib.uoguelph.ca/agricola), Medline (OvidSP; http://ovidsp.tx.ovid.com.subzero.lib.uoguelph.ca), and Web of Science (https://apps.webofknowledge.com.subzero.lib.uoguelph.ca) databases, with the controlled vocabulary option used where available. Grey literature was searched to find unpublished data using Searchable Proceedings of Animal Conferences (S-PAC; https://spac.adsa.org) as well as ProQuest Dissertations and Theses Database (https://search-proquest-com.subzero.lib.uoguelph.ca/pqdt/dissertations) and Open Access Theses and Dissertations (https://oatd.org/). The literature search was conducted between April 4 and 14, 2017, and limited to English language publications. Search results were uploaded to EndNoteX7 (Clarivate Analytics, Philadelphia, PA) and duplicate results documented and removed. No restriction on publication date was

placed aside from that of the database (Agricola, 1970; Medline, 1950; Web of Science, 1900; S-PAC, 1935; ProQuest, 1997; Open Access, 1990). Ten relevant studies were preselected by T. F. Duffield and the search results checked to ensure these studies were included. A research librarian (A. Versluis) with the University of Guelph was consulted on the search strategy.

Search Strategy

Search terms were "calf OR calves OR cattle OR bovine OR dairy OR beef OR Holstein OR Friesian OR Jersey OR ruminant" AND "disbud* OR dehorn* OR cautery OR electric OR rhinehart OR rhinehardt OR iron OR portasol OR express OR buddex OR propane OR butane OR torch" AND "freezing OR numbing OR local OR anesthetic OR anesthetic OR lidocaine OR block OR bupivacaine OR lignocaine OR NSAID OR metacam OR meloxicam OR flunixin OR banamine OR ketoprofen OR anafen OR nonsteroidal anti-inflammatory OR anti-inflammatory OR analgesia OR pain control OR pain mitigation OR meclofenamic acid OR phenylbutasone OR bute OR carprofen OR salicylic acid OR ASA OR aspirin OR naproxen OR tolfenamic acid OR metamizaole sodium."

Study Selection

Studies were exported from EndNoteX7 into DistillerSR (Evidence Partners Inc., Ottawa, ON, Canada) for 2 rounds of screening. A primary round was conducted independently by C. L. Miltenburg and C. B. Winder, assessing the title and abstract for relevance using the questions:

1) Does the title or abstract describe a primary experimental intervention study?
2) Does the title or abstract describe a study involving calves disbudded by cautery?
3) Does the title or abstract describe one or more of the following intervention groups: local anesthetic, NSAID, or local anesthetic and NSAID?

Studies were excluded if both reviewers agreed that the study did not fulfill 1 or more of these criteria. An unclear option was available for all questions, with the study proceeding to full-text screening if all answers were either yes or unclear. Conflicts between inclusion and exclusion by the 2 reviewers were resolved by consensus. Secondary screening was conducted on the full text of remaining studies by C. L. Miltenburg and C. B. Winder independently, using the initial 3 questions and the following questions:

4) Does the study describe one or more of the following comparator groups: local anesthetic, NSAID, or no pain control?
5) If xylazine (or another sedative) was given, was it given to both intervention and comparator group?
6) Does the study examine at least one of the following outcomes: plasma cortisol concentration, pain behaviors (at least one of ear flick, head shake, head rub, foot stamp, or tail swish), or sensitivity of the horn bud sensitivity as measured by algometer or von Frey monofilaments?

Studies were excluded if both reviewers said no to 1 of the previous questions; conflicts were resolved by consensus. Study citations and reasons for exclusion at this stage of screening were recorded (see Supplemental File S2; https://doi.org/10.3168/jds.2017-14092). Primary screening (questions 1 to 3) of title abstracts were pilot tested independently by C. L. Miltenburg and C. B. Winder on the first 100 studies identified by the initial search of Medline (via OvidSP). Full-text screening (questions 4 to 6) were pilot tested independently by C. L. Miltenburg and C. B. Winder on 4 studies preselected by T. F. Duffield.

Data Extraction and Data Extraction Items

Data from studies meeting the study selection criteria were independently extracted by C. L. Miltenburg and C. B. Winder using a standardized form, which was pretested on 4 studies preselected by T. F. Duffield. Discrepancies in data extraction were resolved by consensus.

Study-level data included year published and study period (date or season). Population characteristics consisted of breed, production type (dairy or beef), housing system, commercial or research farm, mean age, sex (male, female, or a mixed group), disbudding method (including disbudding iron type), and disbudding operator (producer, veterinarian, researcher, and so on). Intervention group (including any sham control group) data entailed, for each drug given, drug name, concentration, dose (in mg, mL, or mg/kg), technique (e.g., cornual nerve block) or route (e.g., i.m., i.v., s.c.), and timing relative to disbudding.

Plasma Cortisol Concentration. Outcomes were extracted as continuous measures with the mean for each treatment group and standard deviation. If this was not available, measures of association were collected with standard error or 95% confidence interval, and if a statistical model was used all additional variables included were recorded. We collected the number of

animals in each treatment group, total number of sampling time points, time points relative to disbudding, and whether catheterization or venipuncture was used to obtain samples. If available, data were extracted for each measurement time point individually.

Pain Behaviors. For all individual pain behaviors (ear flick, head shake, head rub, tail swish, foot stamp, and vocalization), outcomes were extracted as continuous measures (number of each behavior within a stated time period) with mean and standard deviation values for each treatment group. If this was not available, measures of association were collected with standard error or 95% confidence interval, and if a statistical model was used all additional variables were included. If data on pain behaviors were recorded for multiple time periods, the data were extracted for each time period. If pain behaviors were only available as a sum of several behaviors, these data were extracted and the type of behaviors summed was recorded. Data at individual time points were preferred; if only summed data for several time points were available, these were extracted. We collected the number of animals in each treatment group, the total number of observation periods, the time of the observation period relative to disbudding, the length of observation periods, and if observation was done live or by video recording.

Horn Bud Sensitivity. Horn bud sensitivity was defined as a behavioral test where pressure is applied to the area around the horn bud, with a reading taken of the pressure measurement (in kilograms of force) at the time at which the calf reacts by either resisting the restraint or moving away from the device. These data were extracted as a continuous measure with mean and standard deviation values for each treatment group. If this was not available, measures of association were collected with standard error or 95% confidence interval, and if a statistical model was used all additional variables were included. If data were recorded for multiple time periods, the data were extracted for each time period. We collected the number of animals in each treatment group, the total number of evaluation time points, the type of measurement (algometry or von Frey monofilaments), and measurement time relative to disbudding. Data from individual time points were preferred, but if only summed data from multiple time points were available, these were collected.

Risk of Bias in Individual Studies

Assessment of bias was done independently by C. L. Miltenburg and C. B. Winder, and was pilot tested by C. L. Miltenburg and C. B. Winder on the same 4 preselected studies chosen by T. F. Duffield for data extraction testing. Disagreements were resolved by consensus. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al., 2011), modified by also including an assessment of reporting of randomization (in addition to random sequence generation). Risk of bias was assessed for each outcome class [plasma cortisol concentration, pain behaviors (as a group), and horn bud sensitivity].

Summary Measures and Synthesis of Results

If more than 2 studies reported the same outcome at a similar time point or period with the same comparison groups, meta-analysis was conducted. Similar time points initially were predefined in the review protocol as not more than 10 min difference during the first 70 min after disbudding and within 20 min after this time. For plasma cortisol concentration and pressure sensitivity, this definition was kept. The original definition of similar time point was also kept for pain behavior measures within the first 60 min after disbudding. However, due to the large variability in time points measuring pain behaviors between studies, time points at 1 h or later from disbudding were considered similar if measured within 60 min for the first 3 h and within 120 min thereafter. Similar time period applied to pain behavior observation windows, the larger of which was initially defined as no more than 150% of the smaller window. Due to the variability of time periods used in studies measuring pain behaviors, this was expanded to include all time periods, which ranged from 5 to 60 min of observation or video recording per period. If more than 1 outcome measure was reported within a similar time period for a single study, the time closest to the midpoint of the similar time period was used for meta-analysis. This ensured that observations within a similar time period were independent. For outcomes that were measured on the same continuous scale, mean differences were used. If different scales were used (e.g., ear flicks per 10 min and ear flicks per 15 min), standardized mean differences (**SMD**) were used.

All meta-analysis was done in R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio version 1.0.136 (RStudio Inc., Boston, MA) with the 'metafor' package (Viechtbauer, 2010). Meta-analysis used a random effects approach, and weighting of primary studies was done using the inverse variance method. Random effects models were chosen, as it was assumed study-specific differences may exist and thus studies may not all measure the same true effect. Heterogeneity between studies was assessed with the I^2 statistic (Viechtbauer, 2010). Heterogeneity was to be explored via subgroup analysis or meta-regression if enough studies were found for a single outcome.

A subgroup analysis was planned for those with and without the use of xylazine sedation for each intervention comparator group (if there were at least 3 studies in each group). For treatment group comparisons of outcomes lacking at least 2 studies, data were reported as a narrative synthesis (Table 1).

Risk of Bias at the Review Level

If 10 or more studies were found for a single outcome, a funnel plot (effect estimate versus the inverse of its standard error) was used to visually assess potential for publication bias (Viechtbauer, 2010).

RESULTS

Study Selection and Characteristics

Results of the search strategy and study selection are presented in Figure 1. Seventy-five full-text articles were reviewed, with 54 not meeting eligibility criteria and 21 articles containing 23 separate experiments included in the qualitative synthesis. Details of the 21 studies remaining after full-text screening are listed in Table 1. A list of studies excluded at the full-text screening stage is available in Supplemental File S3 (https://doi.org/10.3168/jds.2017-14092).

Relevant Interventions and Comparator Groups

Of the 21 included studies, 12 contained an intervention group receiving local anesthetic with a comparator of saline or no treatment; these comprised 13 local anesthetic treatment groups. Fourteen studies included an intervention group receiving an NSAID in addition to local anesthetic with a comparator of local anesthetic only; these compromised 22 treatment groups. One study had a treatment group of calves receiving NSAID alone with a comparator group of no treatment (Stilwell, 2009). Two studies used xylazine sedation given to both intervention and comparator groups; one of these studies compared local anesthetic to saline (Stilwell et al., 2010), whereas the other compared local anesthetic and ketoprofen to local anesthetic alone (Faulkner and Weary, 2000).

Data Extraction from Figures

Data extraction deviated from the a priori protocol for those studies not reporting values numerically, but which had data available as a graph with a measure of variation. These values were extracted independently by both C. L. Miltenburg and C. B. Winder using WebPlotDigitizer version 3.12 (Rohatgi, 2017). Initial differences between values were discussed and graphs were re-examined to ensure errors had not been made; further, smaller, discrepancies in values were averaged. Plasma cortisol data from 10 of 15 studies were only available graphically, as were data from 5 of 7 studies reporting pain behaviors and data from all 4 studies reporting pressure sensitivity.

Synthesis of Study Results by Outcome Type

Forest plots for all meta-analyses conducted are available in Supplemental File S4 (https://doi.org/10.3168/jds.2017-14092); a summary of the overall effect measures for each meta-analyses conducted for different time points for the same intervention/comparator and the same outcome are included as figures (Figure 2, 3, 4, 5, and 6).

Plasma Cortisol Concentration. Although 18 studies reported measuring plasma cortisol concentration, only 15 were included in meta-analyses. Grøndahl-Nielsen et al. (1999) reported only maximum cortisol values. Stock et al. (2015) reported maximum cortisol values, area under the effect curve for 0 to 24, 24 to 96, and 0 to 96 h postdisbudding, and percent change in cortisol from baseline over the same time periods. Huber et al. (2013) did not report any measure of variability. Therefore, these 3 studies were excluded from the meta-analysis.

Sampling was done via jugular venipuncture in 7 studies, jugular catheters in 7 studies, and was unreported in 1 study. Units of measurement were not uniform between studies; absolute values (in both nmol/L and ng/mL) were reported as well as change from baseline and back-transformed geometric means. As a result, SMD were used for all plasma cortisol-related meta-analyses.

For studies included in the meta-analyses, time points were considered as described above, where 3 or more studies compared the same intervention at a similar time. For the comparison of local anesthetic to saline or no treatment, 7 treatment groups were used at 30 min, 8 treatment groups at 1 h, 4 treatment groups at 2 h, 5 treatment groups at 3 h, 5 treatment groups at 4 h, 4 treatment groups at 6 h, and 4 treatment groups at 24 h postdisbudding. For studies reporting plasma cortisol concentration at 30 min or 1 h postdisbudding, a significant protective effect of local anesthetic was seen (Figure 2), but substantial heterogeneity existed among studies ($I^2 > 50\%$). For studies reporting plasma cortisol concentration at 2 or 3 h postdisbudding, no effect of treatment on cortisol was observed and heterogeneity was moderate ($I^2 = 43\%$ for both 2 and 3 h). At 4 h postdisbudding, treatment with local anesthetic resulted in higher cortisol concentrations than saline or no treatment and substantial heterogeneity among

Table 1. Characteristics of the 21 studies included in the systematic review on the effects of local anesthesia or nonsteroidal anti-inflammatory drug (NSAID) analgesia on pain associated with cautery disbudding in dairy calves, after full-text screening[1]

Study	Experiment	Population	Relevant intervention group	Randomization/ method/blinding	Relevant outcome	Data from figures
Allen et al. (2013)	1	Male Holstein calves 8 to 10 wk of age	Lidocaine HCl 2% (5 mL) cornual nerve block 15 min predisbudding, 1 mg/kg of oral meloxicam 12 h predisbudding; Lidocaine HCl 2% (5 mL) cornual nerve block 15 min predisbudding, 1 mg/kg of oral meloxicam at disbudding	Y/Y/NR; Y/Y/NR	Plasma cortisol (5, 30, 60, 120, 240, 360, 480, and 720 min postdisbudding) Pressure sensitivity (60, 120, 240, 360, 480, and 720 min, 1, 2, 3, 4, 5, 6, and 7 d postdisbudding)	Y; Y
Boandl et al. (1989)	1	Female Holstein calves 7 to 16 wk of age	Lidocaine HCl 2% (5 mL) cornual nerve block 5 min predisbudding	NR/NR/NR	Plasma cortisol (30 min postdisbudding)	N
Doherty et al. (2007)	1	Female Holstein-Friesian calves 10 to 12 wk of age	Lidocaine 5% (5 mL) cornual nerve block and 2 additional sites	Y/NR/NR	Plasma cortisol (30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 48, and 72 h postdisbudding)	Y
Doherty et al. (2007)	1	Female Holstein-Friesian calves 10 to 12 wk of age	Lidocaine 2% (5 mL) cornual nerve block and 2 additional sites	Y/NR/NR	Pain behavior (head rub; scan sampling for 72 h postdisbudding)	NA
Duffield et al. (2010)	1	Female Holstein calves 4 to 8 wk of age	Lidocaine HCl 2% with epinephrine (5 mL) cornual nerve block 10 min predisbudding, 3 mg/kg of ketoprofen i.m. 10 min predisbudding	Y/NR/Y; Y/NR/Y	Plasma cortisol (3 and 6 h postdisbudding); Pain behavior (ear flick, head shake, head rub; 20-min periods at 1, 3, 4, 6, and 7 h postdisbudding)	Y; Y
Faulkner and Weary (2000)	1	Female and male Holstein calves 4 to 8 wk of age	Lidocaine HCl 2% (4.5 mL) as a cornual nerve block and ring block 10 min predisbudding, 3 mg/kg of ketoprofen 2 h predisbudding, and 2 and 7 h postdisbudding, 0.2 mg/kg of xylazine 20 min predisbudding	N/NA/Y	Pain behavior (ear flick, head shake, head rub; 20-min periods at 1, 2, 3, 4, 6, 9, 12, and 24 h postdisbudding)	Y
Graf and Senn (1999)	1	Pure and mixed-bred female and male dairy calves 4 to 6 wk of age	Lidocaine 2% (8 mL) cornual nerve block and 1 additional site 20 min predisbudding	NR/NR/Y	Pain behavior (head shake; continuous sampling hourly at 1, 2, 3, and 4 h postdisbudding)	N
Graf and Senn (1999)	2	Female and male pure and mixed-bred dairy breed calves 4 to 6 wk of age	Lidocaine 2% (8 mL) cornual nerve block and 1 additional site 20 min predisbudding	NR/NR/NR	Plasma cortisol (5, 10, 20, 40, 60, 90, 120, 150, 180, 210, and 240 min postdisbudding)	Y
Grøndahl-Nielsen et al. (1999)	1	Female and male Friesian calves 4 to 6 wk of age	Lidocaine 2% cornual nerve block 15 min predisbudding	Y/NR/NR; Y/NR/NR	Plasma cortisol (5, 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 210, and 240 min postdisbudding); Pain behavior (head shake, ear flick; scan sampling for 15-min periods over 4 h postdisbudding)	NA; NA
Heinrich et al. (2009)	1	Female Holstein calves 6 to 12 wk of age	Lidocaine HCl 2% with epinephrine (5 mL) cornual nerve block 10 min predisbudding, 0.5 mg/kg of meloxicam i.m. 10 min predisbudding	Y/NR/NR	Plasma cortisol (30 min, 1, 1.5, 2, 4, 6, and 24 h postdisbudding)	Y

Continued

Table 1 (Continued). Characteristics of the 21 studies included in the systematic review on the effects of local anesthesia or nonsteroidal anti-inflammatory drug (NSAID) analgesia on pain associated with cautery disbudding in dairy calves, after full-text screening[1]

Study	Experiment	Population	Relevant intervention group	Randomization/ method/blinding	Relevant outcome	Data from figures
Heinrich et al. (2010)	1	Female Holstein calves mean 9 (±1) wk of age	Lidocaine HCl 2% with epinephrine (5 mL) cornual nerve block 10 min predisbudding, 0.5 mg/kg of meloxicam i.m. 10 min predisbudding	Y/NR/Y; Y/NR/Y	Pain behavior (ear flick, head rub, head shake, foot stamp; 1-h periods at 2, 4, 6, 9, 20, 26, 28, 30, 33, and 44 h postdisbudding); Pressure sensitivity (4 h postdisbudding)	Y; Y
Huber et al. (2013)	1	Female and male dairy breed calves 5 to 9 wk of age	Procaine HCl 2% (10 mL) cornual nerve block 20 min predisbudding, 2.2 mg/kg of flunixin meglumine i.v. at disbudding; Procaine HCl 2% (10 mL) cornual nerve block 20 min predisbudding, 2.2 mg/kg of flunixin meglumine i.v. at disbudding and 3 h postdisbudding	Y/Y/Y; Y/Y/Y	Plasma cortisol (30 min and 1, 2, 4, 6, and 8 h postdisbudding); Pain behavior (head shake, head rub, ear flick, foot stamp; 5-min periods at 30 min and 1, 2, 4, 6, and 8 h postdisbudding)	NA; NA
Korkmaz et al. (2015)	1	Male Holstein-Friesian calves 6 to 8 wk of age	Lidocaine HCl 2% with epinephrine (6 mL) cornual nerve block 20 min predisbudding, 2.0 mg/ kg of dexketoprofen i.v. 30 min predisbudding	Y/NR/NR	Plasma cortisol (30, 50, and 60 min postdisbudding)	N
Milligan et al. (2004)	1	Female and male Holstein calves mean 7 (±1) d of age	Lidocaine HCl 2% with epinephrine (5 mL) cornual nerve block 10 min predisbudding, 3.0 mg/kg of ketoprofen i.m. 10 min predisbudding	Y/NR/Y; Y/NR/Y	Plasma cortisol (3 and 6 h postdisbudding); Pain behavior (ear flick, head shake, head rub; 60-min scan sampling per period for 0 to 2, 3 to 5, and 6 to 8 h postdisbudding)	N; N
Mintline et al. (2013)	1	Female and male Holstein-Friesian calves 4 to 6 wk of age	Lignocaine HCl 2% (5 mL) cornual nerve block and ring block 10 min predisbudding; Lignocaine HCl 2% (5 mL) cornual nerve block and ring block 10 min predisbudding, 0.5 mg/kg of meloxicam i.v. 55 min predisbudding	Y/NR/Y	Pressure sensitivity (3, 27, 51, and 75 h postdisbudding)	NA
Morisse et al. (1995)	1	Male Montbéliarde calves 8 wk of age	Lignocaine 2% (4 mL) cornual nerve block 15 min predisbudding	NR/NR/NR	Pain behavior (head shake, head rub, head scratch, tail flap; sum of 4 h postdisbudding)	NA
	2	Male Montbéliarde calves 8 wk of age	Lignocaine 2% (4 mL) cornual nerve block 15 min predisbudding	NR/NR/NR	Plasma cortisol (1, 4, and 24 h postdisbudding)	Y
Petrie et al. (1996)	1	Male Friesian calves 6 to 8 wk of age	Lignocaine HCl 2% (3 mL) cornual nerve block 20 min predisbudding	Y/NR/NR	Plasma cortisol (15, 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, and 480 min postdisbudding)	Y
Stilwell (2009)	Study 7 experiment 2	Female dairy calves mean 75 (±9) d of age	Lidocaine 2% (5 mL) cornual nerve block 15 min predisbudding; Lidocaine 2% (5 mL) cornual nerve block 15 min predisbudding, 1.4 mg/kg of carprofen i.v. 15 min predisbudding; 1.4 mg/kg of carprofen i.v. 15 min predisbudding	Y/NR/NR; Y/NR/Y	Plasma cortisol (10, 30, and 50 min postdisbudding); Pain behavior (ear flick, head shake, head rub, transitions; 10, 30, and 50 min postdisbudding)	N

Continued

Table 1 (Continued). Characteristics of the 21 studies included in the systematic review on the effects of local anesthesia or nonsteroidal anti-inflammatory drug (NSAID) analgesia on pain associated with cautery disbudding in dairy calves, after full-text screening[1]

Study	Experiment	Population	Relevant intervention group	Randomization/ method/blinding	Relevant outcome	Data from figures
Stilwell et al. (2010)	1	Female Holstein calves mean 37 (±4) d of age	Lidocaine 2% (5 mL) cornual nerve block 8 min predisbudding, 0.2 mg/kg of xylazine i.m. 10 min predisbudding	Y/NR/Y; Y/NR/Y	Plasma cortisol (10, 25, 40, and 60 min postdisbudding); Pain behavior (ear flick, head shake, head rub; 5-min periods at 10, 25, 40, and 60 min postdisbudding)	N; Y
Stilwell et al. (2012)	1	Female dairy breed calves mean 88 (±17) d of age	Lidocaine 2% (5 mL) cornual nerve block 15 min predisbudding; Lidocaine 2% (5 mL) cornual nerve block 15 min predisbudding, 1.4 mg/kg of carprofen i.v. 15 min predisbudding	Y/NR/NR; Y/NR/Y	Plasma cortisol (1, 3, 6, and 24 h postdisbudding); Pain behavior (head shake, head rub, ear flick; 15 min and 1, 3, 6, and 24 h postdisbudding)	Y; Y
Stock et al. (2015)	1	Female and male Holstein calves mean 33 (±4) d of age	Lidocaine 2% (5 mL) cornual nerve block 10 min predisbudding, 0.5 mg/kg of firocoxib oral 10 min predisbudding	Y/Y/NR; Y/Y/NR	Plasma cortisol (15, 30 min and 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 h postdisbudding); Pressure sensitivity (2, 4, 6, 8, and 24 h postdisbudding)	Y; Y
Stock (2015)	Chapter 6	Female calves mean 51 d of age (range 41 to 60)	Lidocaine 2% (5 mL) cornual nerve block 5 min predisbudding, 2.0 mg/kg of carprofen oral 5 min predisbudding; Lidocaine 2% (5 mL) cornual nerve block 5 min predisbudding, 2.0 mg/kg of firocoxib oral 5 min predisbudding; Lidocaine 2% (5 mL) cornual nerve block 5 min predisbudding, 2.3 mg/kg of flunixin meglumine oral 5 min predisbudding; Lidocaine 2% (5 mL) cornual nerve block 5 min predisbudding, 2.0 mg/kg of meloxicam oral 5 min predisbudding	Y/Y/NR; Y/Y/NR	Plasma cortisol (4, 8, 24, 48, 96, 144, and 192 h postdisbudding); Pressure sensitivity (4, 8, 24, 48, 96, 144, and 192 h postdisbudding)	NA; NA
Stock et al. (2016)	1	Female and male Holstein calves mean 51 (±5) d of age	Lidocaine 2% (5 mL) cornual nerve block 10 min predisbudding, 1.4 mg/kg of carprofen s.c. 10 min predisbudding; Lidocaine 2% (5 mL) cornual nerve block 10 min predisbudding, 1.4 mg/kg of carprofen oral 10 min predisbudding	Y/Y/NR; Y/Y/NR	Plasma cortisol (30, 45 min and 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 h postdisbudding); Pressure sensitivity (4, 8, 12, 24, 48, 72, and 96 h postdisbudding)	Y; Y

[1]Randomization reflects whether the authors reported any attempt to randomly assign animals to treatment group. Method refers to whether the method of randomization was reported. Blinding refers to blinding of outcome assessors. Figure data refers to whether data were not available and required extraction from figures (WebPlotDigitizer version 3.12; Austin, TX; Rohatgi, 2017). Y = yes, N = no, NA = not applicable, NR = not reported or insufficient detail to assess.

studies was present ($I^2 > 50\%$). For studies reporting cortisol at 6 h or 24 h, we found no effect of treatment and heterogeneity was again present ($I^2 > 50\%$).

For the comparison of local anesthetic and NSAID to local anesthetic alone, 8 treatment groups were used at 30 min, 9 treatment groups were used at 1 h, 6 treatment groups were used at 2 h, 3 treatment groups at 3 h, 6 treatment groups at 4 h, and 9 treatment groups at 6 h, and 7 treatment groups at 24 h postdisbudding. For studies reporting plasma cortisol at 30 min and 1,

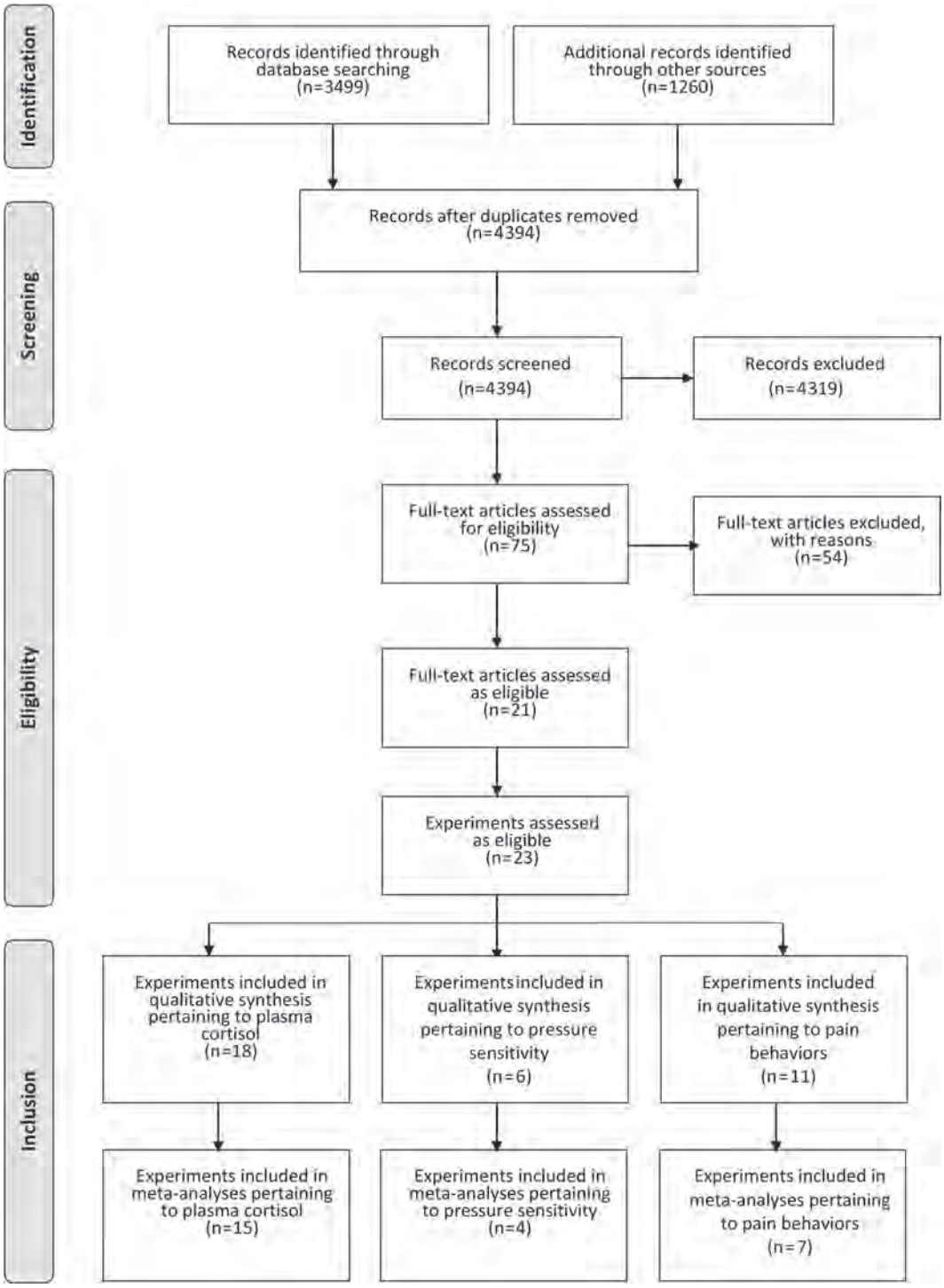

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram (Moher et al., 2010).

2, or 3 h postdisbudding, no effect of treatment and no heterogeneity was observed (I^2 = 0%; Figure 3). For studies reporting cortisol at 4 h postdisbudding, a protective effect was detected, with moderate heterogeneity between studies (I^2 = 44%). For studies reporting at 6 h postdisbudding, no overall treatment effect was present and heterogeneity was low (I^2 = 17%). At 24 h postdisbudding, plasma cortisol concentration was greater in calves that received local anesthesia and NSAID and we noted moderate heterogeneity (I^2 = 46%).

Pressure Sensitivity. Six studies reported measuring pressure sensitivity, either using a pressure algometer (Heinrich et al., 2010; Allen et al., 2013; Stock, 2015; Stock et al., 2015, 2016) or VonFrey monofilaments (Mintline et al., 2013). Two of these studies were not used in the meta-analyses. Mintline et al. (2013) did not report a measure of variability among treatment groups. Stock (2015) reported percent change in algometry score at 24 and 192 h and could not be combined. Three studies reported absolute values (kgf) whereas 1 reported back-transformed geometric means, and therefore SMD were used in pressure sensitivity related meta-analyses.

Of the 4 studies included in the meta-analyses, only comparisons between local anesthesia with NSAID and local anesthesia alone were examined. Time points were considered as described in the methods, where 3 or more studies compared the same intervention at a similar time. Three treatment groups were used at 2 h, 6 treatment groups at 4 h, 3 treatment groups at 6 h, 5 treatment groups at 8 h, 4 treatment groups at 12 h, 5 treatment groups at 24 h, and 4 treatment groups at 48, 72, and 96 h postdisbudding (Figure 4). For studies reporting pressure sensitivity at 2 h postdisbudding, no effect of treatment was seen and moderate heterogeneity was present between studies (I^2 = 37%). For studies reporting at 4 or 6 h postdisbudding, an overall effect was seen with calves treated with NSAID in addition to local anesthetic tolerating more pressure on the areas around their horn bud. No heterogeneity was seen

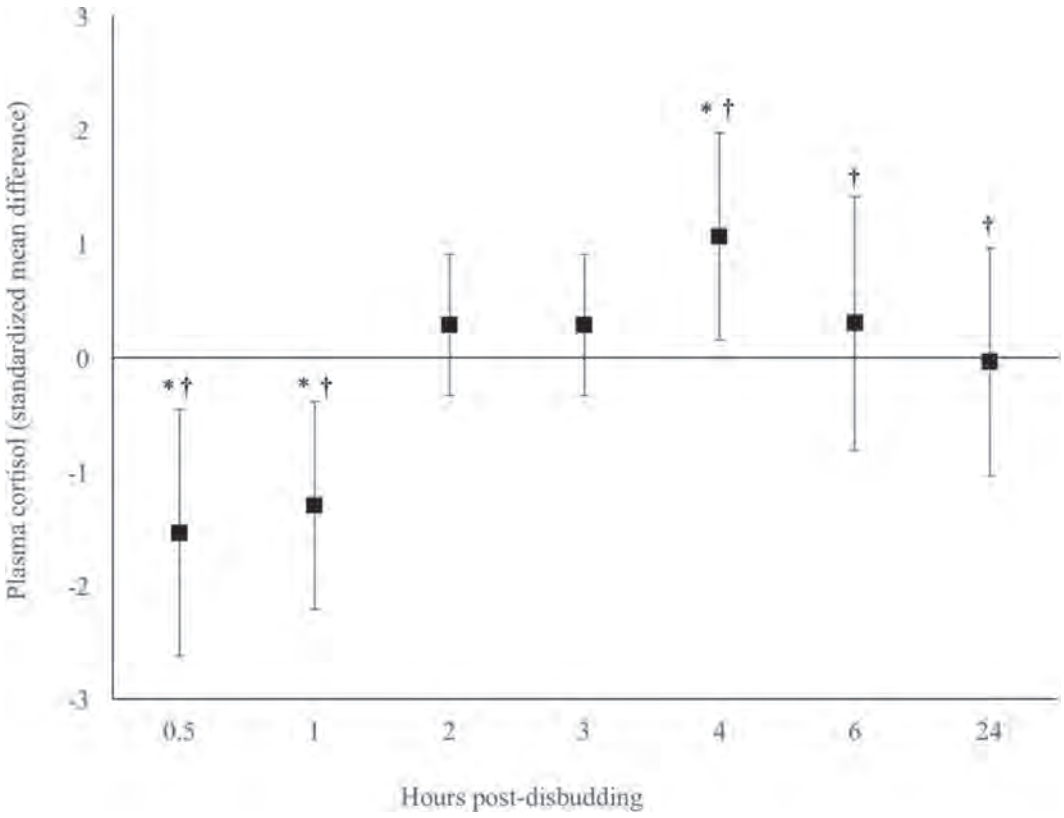

Figure 2. Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anesthesia compared with control on standardized mean difference in plasma cortisol at time points 0.5 h (5 studies; 7 comparison groups; 122 calves; I^2 = 83%), 1 h (7 studies; 8 comparison groups; 135 calves; I^2 = 80%), 2 h (4 studies; 5 comparison groups; 76 calves), 3 h (4 studies; 5 comparison groups; 76 calves), 4 h (4 studies; 5 comparison groups; 87 calves; I^2 = 72%), 6 h (3 studies; 4 comparison groups; 60 calves; I^2 = 75%), and 24 h (3 studies, 4 comparison groups; 69 calves; I^2 = 74%) postdisbudding. An asterisk (*) indicates a significant overall effect of treatment ($P < 0.05$); a dagger (†) indicates substantial heterogeneity ($I^2 > 50\%$) within a meta-analysis.

between studies at these 2 time points ($I^2 = 0\%$). For all further time points (8, 12, 24, 48, 72, or 96 h), no effect of treatment was observed, and we noted low heterogeneity between studies ($I^2 = 0$–20%).

Pain Behavior. Eleven studies reported measuring at least 1 pain-related behavior (ear flick, head shake, head rub, tail swish, foot stamp, or vocalization); 7 of these studies were included in the meta-analyses. Stilwell (2009) reported combined values for ear flick, head shake, head rub, and quick transitions from standing to laying and could not be combined with results from other studies. Morisse et al. (1995) reported total frequency of behaviors by treatment group for the first 4 h postdisbudding, with no measure of variability. Huber et al. (2013) and Grøndahl-Nielsen et al. (1999) also did not report any measures of variability.

Three studies with 3 treatments (Graf and Senn, 1999; Stilwell et al., 2010; Stilwell et al., 2012) compared local anesthesia and saline or no treatment. Both studies by Stilwell et al. (2010; 2012) reported ear flick, head shake, and head rub using live observation over 5- (Stilwell et al., 2010) and 15-min (Stilwell et al., 2012) periods. Graf and Senn (1999) reported head shakes using video recording over 60-min periods. Only 1 time point for 1 pain behavior, head shakes at 1 h postdisbudding, could be combined in a meta-analysis. This synthesis showed no overall treatment effect of reduction in mean head shakes (SMD = −0.58; 95% CI = −1.17–0.01), with low heterogeneity between studies ($I^2 = 11\%$).

Five studies with 5 treatments compared local anesthesia and NSAID to local anesthesia alone; 3 used video recording whereas 2 employed live observations. Recording period length ranged from 15 to 60 min. Three studies reported ear flick, head shake, and head rub, 1 reported ear flick and head shake, and 1 reported only ear flick. For ear flick, 4 treatment groups were compared at 1 h, 3 treatment groups at 3 h, 4 treatment groups at 4 h, 5 treatment groups at 6 h, and 3 treatment groups at 24 h postdisbudding (Figure 5). For studies reporting ear flicks at 1 h postdisbudding, no treatment effect was seen, with substantial hetero-

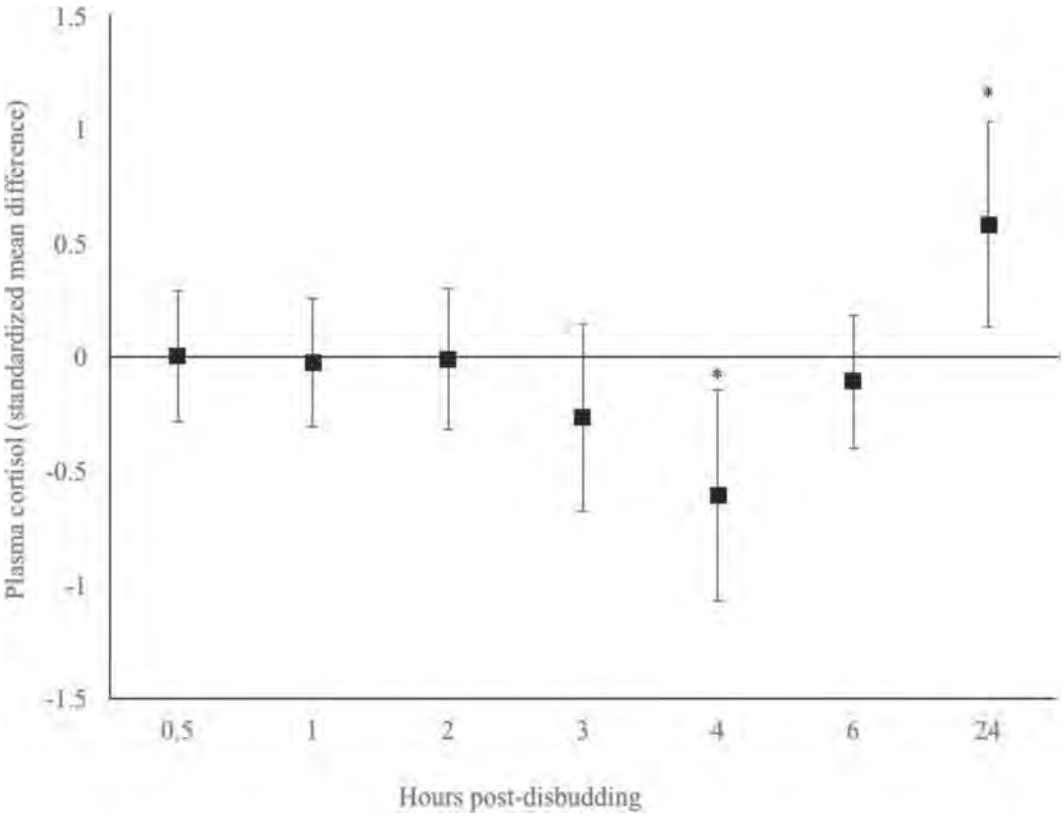

Figure 3. Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anesthesia and nonsteroidal anti-inflammatory drugs (NSAID) compared with local anesthesia on standardized mean difference in plasma cortisol at time points 0.5 h (6 studies; 8 comparison groups; 186 calves), 1 h (7 studies; 9 comparison groups; 198 calves), 2 h (4 studies; 6 comparison groups; 160 calves), 3 h (3 studies; 3 comparison groups; 92 calves), 4 h (4 studies; 6 comparison groups; 160 calves), 6 h (7 studies; 9 comparison groups; 252 calves), and 24 h (5 studies, 7 comparison groups; 172 calves; $I^2 = 46\%$) postdisbudding. An asterisk (*) indicates a significant overall effect of treatment ($P < 0.05$).

geneity (I^2 = 90%). For studies reporting ear flicks at 3 or 4 h, a protective effect of treatment was seen, with low heterogeneity (I^2 = 22 and 0% for 3 and 4 h, respectively). At 6 or 24 h, no overall effect of treatment was measured and substantial heterogeneity was present between studies (I^2 >50%).

For head shake, 3 treatment groups were compared at 1 h, 3 treatment groups at 4 h, 4 treatment groups at 6 h, and 3 at 24 h postdisbudding (Figure 6). For studies reporting head shake at 1 h postdisbudding, no effect of treatment was seen, with no heterogeneity present between studies (I^2 = 0%). For studies reporting at 4 or 6 h postdisbudding, a protective effect of treatment was found with no heterogeneity between studies (I^2 = 0%). For studies reporting at 24 h postdisbudding, no overall treatment effect was seen, although substantial heterogeneity was present between studies (I^2 = 59%).

For head rub, 3 treatment groups were compared at 6 h postdisbudding and no effect of treatment was observed (SMD = −0.24; 95% CI = −0.71–0.23). No heterogeneity was detected between studies (I^2 = 0%).

Subgroup Analysis, Meta-Regression, and Publication Bias

Xylazine sedation was identified a priori as a possible subgroup of studies; however, as only 2 studies were included with this treatment, each with a different intervention or comparator group, no subgroup analysis was possible. During data extraction the NSAID treatments were recorded for possible subgroup analysis. Too much variability was present to have enough similar treatments for subgroup analysis, however (see Table 2). Six NSAID products were given via 4 routes, in some cases at different dosages, and at a range of time points. As fewer than 10 studies were used in all meta-analyses, no meta-regression was attempted, nor were funnel plots used to detect possible publication bias.

Assessment of Risk of Bias Across Studies

All studies failed to report pertinent information in at least 1 section in the risk of bias assessment. Al-

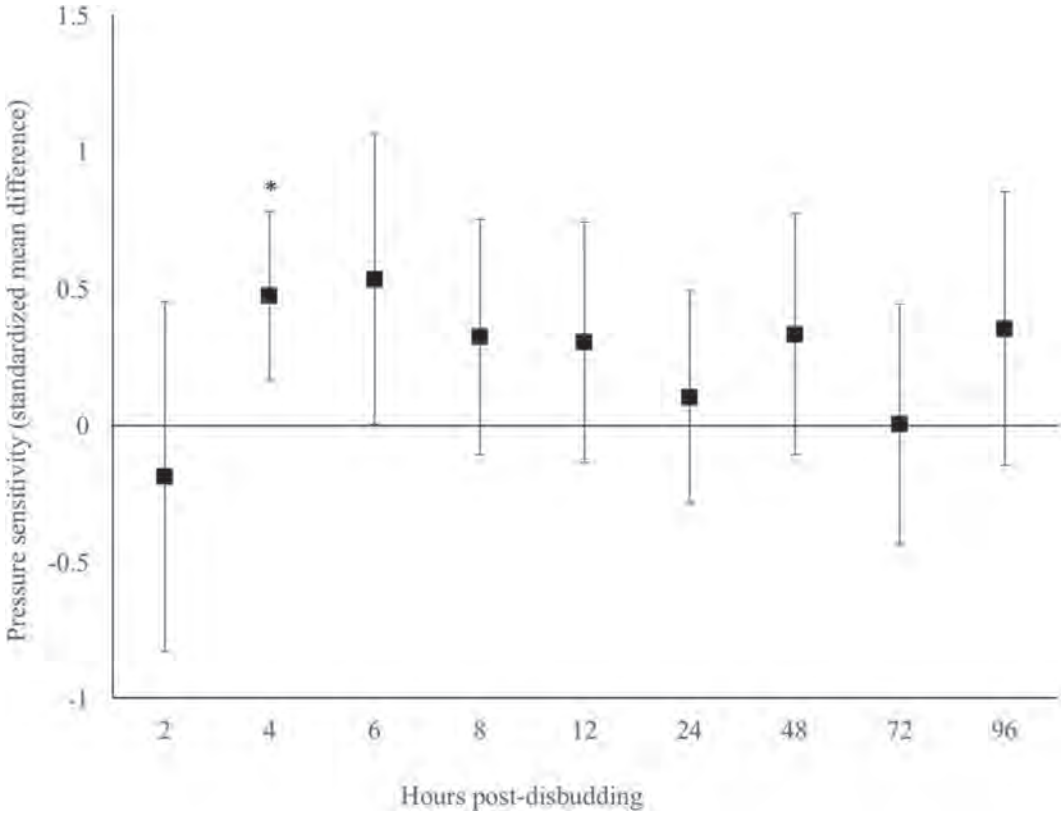

Figure 4. Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anesthesia and nonsteroidal anti-inflammatory drugs (NSAID) compared with local anesthesia on standardized mean difference in horn bud pressure sensitivity at time points 2 h (2 studies; 3 comparison groups; 60 calves), 4 h (4 studies; 6 comparison groups; 160 calves), 6 h (2 studies; 3 comparison groups; 60 calves), 8 h (3 studies; 5 comparison groups; 100 calves), 12 h (2 studies; 4 comparison groups; 80 calves), 24 h (3 studies; 5 comparison groups; 100 calves), 48 h (2 studies; 4 comparison groups; 80 calves), 72 h (2 studies; 4 comparison groups; 80 calves), and 96 h (2 studies; 4 comparison groups; 80 calves) postdisbudding. An asterisk (*) indicates a significant overall effect of treatment ($P < 0.05$).

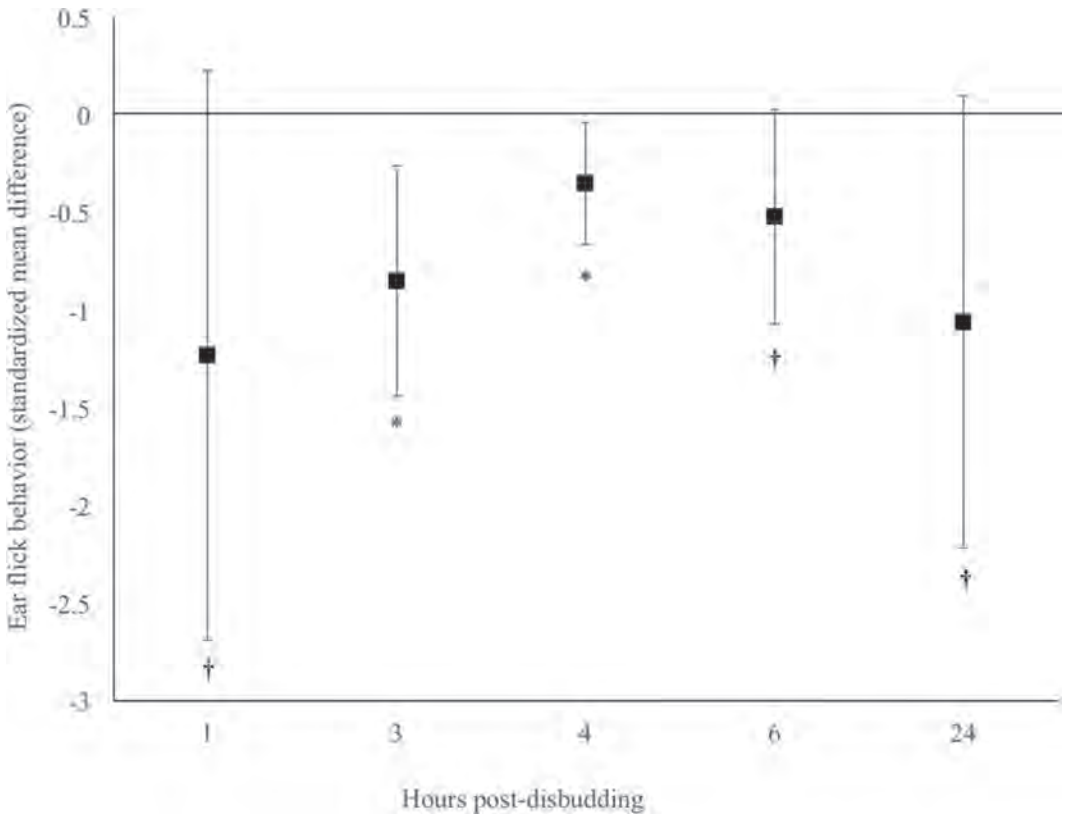

Figure 5. Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anesthesia and nonsteroidal anti-inflammatory drugs (NSAID) compared with local anesthesia on standardized mean difference in ear flick behavior at time points 1 h (4 studies; 4 comparison groups; 132 calves; $I^2 = 90\%$), 3 h (3 studies; 3 comparison groups; 72 calves), 4 h (4 studies; 4 comparison groups; 160 calves), 6 h (5 studies; 5 comparison groups; 172 calves; $I^2 = 63\%$), and 24 h (3 studies; 3 comparison groups; 92 calves; $I^2 = 78\%$) postdisbudding. An asterisk (*) indicates a significant overall effect of treatment ($P < 0.05$); a dagger (†) indicates substantial heterogeneity ($I^2 > 50\%$) within a meta-analysis.

though 17 studies reported randomization of calves to treatment groups, 12 did not report the method of randomization. Method of allocation concealment was only reported in 1 study. Blinding of outcome assessment was reported for 19 of 35 outcomes. Whereas data may or may not have been combinable based on how they were reported, all studies did report some form of outcome data for all outcomes listed in the studies' materials and methods sections.

DISCUSSION

Effect of Local Anesthetic Compared with Saline or No Treatment

Our findings illustrate that the provision of local anesthetic was associated with an initial protective effect on plasma cortisol, with a negative effect seen in studies evaluating cortisol after the duration of anesthesia, after which treatment and control groups were not different. This rise in cortisol observed in the treatment group after anesthesia has been postulated to be due to inflammatory pain, which may be reduced in control calves, as their initial cortisol spike may result in a dampening of the inflammatory response as compared with calves without this initial rise (Stock et al., 2013).

The heterogeneity among studies at 30 min and 1, 4, 6, and 24 h postdisbudding, indicated inconsistency of effect between studies, which may be due to numerous factors, including random variation as well as contextual and methodological variation. Even with 7 and 8 studies included in the meta-analyses, total sample size was only 60 to 70 calves per treatment group; random variation within these populations due to the small sample size may account for some of the between-study variability. Additionally, plasma cortisol could have been influenced by many other factors than use of pain control, such as differences in handling methods, time of day of sample collection, diameter of disbudding iron, and resultant wound size, as well as factors associated with the pain control itself (percentage of active ingredient, volume used, technique used, if epinephrine

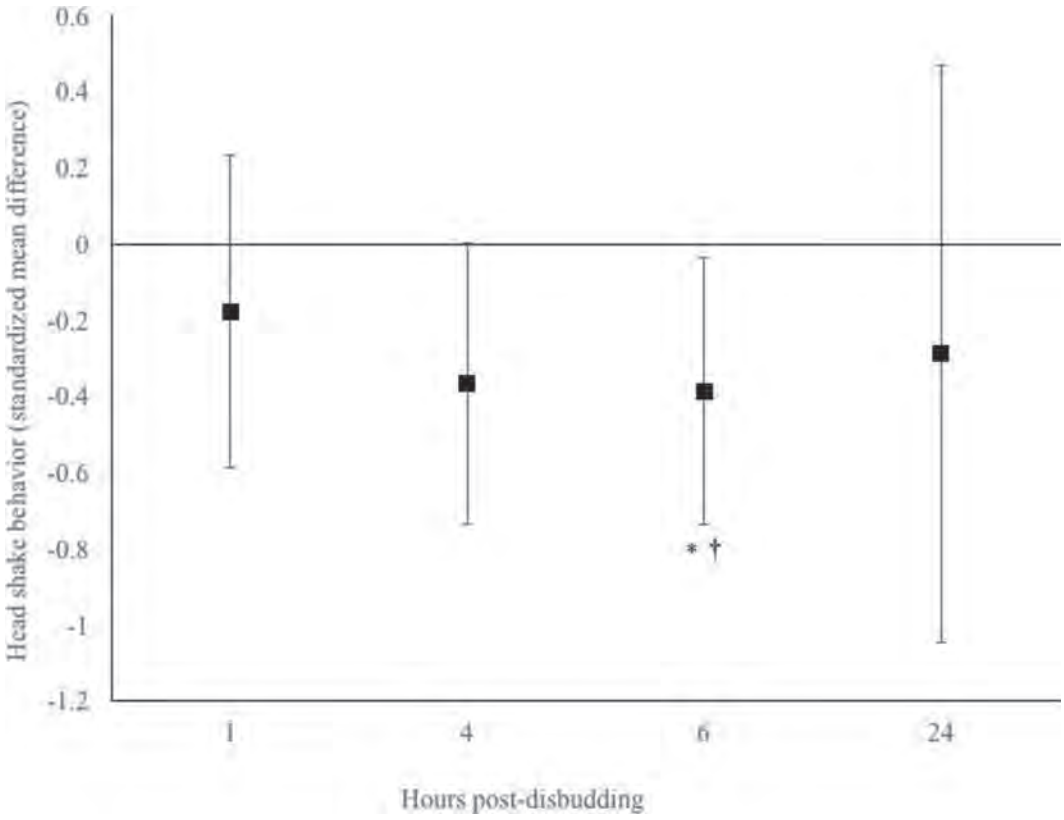

Figure 6. Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anesthesia and nonsteroidal anti-inflammatory drugs (NSAID) compared with local anesthesia on standardized mean difference in head shake behavior at time points 1 h (3 studies; 3 comparison groups; 92 calves), 4 h (3 studies; 3 comparison groups; 120 calves), 6 h (4 studies; 4 comparison groups; 132 calves), and 24 h (3 studies; 3 comparison groups; 92 calves) post-disbudding. An asterisk (*) indicates a significant overall effect of treatment ($P < 0.05$); a dagger (†) indicates substantial heterogeneity (percentage of variation across studies beyond chance, $I^2 > 50\%$) within a meta-analysis.

Table 2. Nonsteroidal anti-inflammatory drug (NSAID) protocols among the 17 treatment trials that compared local anesthetic and NSAID to local anesthetic alone, which were included after full-text screening

NSAID	Study	Route	Dose	Time
Carprofen	Stilwell (2009)	i.v.	1.4 mg/kg	15 min predisbud
	Stilwell et al. (2012)	i.v.	1.4 mg/kg	15 min predisbud
	Stock et al. (2015)	Oral	2.0 mg/kg	5 min predisbud
	Stock et al. (2016)	s.c.	1.4 mg/kg	10 min predisbud
	Stock et al. (2016)	Oral	1.4 mg/kg	10 min predisbud
Dexketoprofen	Korkmaz et al. (2015)	i.v.	3.0 mg/kg	30 min predisbud
Firocoxib	Stock et al. (2015)	Oral	0.5 mg/kg	10 min predisbud
	Stock (2015)	Oral	2.0 mg/kg	5 min predisbud
Flunixin meglumine	Huber et al. (2013)	i.v.	2.2 mg/kg	At disbudding
	Huber et al. (2013)	i.v.	2.2 mg/kg	At disbudding, 3 h postdisbud
	Stock (2015)	Oral	2.3 mg/kg	5 min predisbud
Ketoprofen	Duffield et al. (2010)	i.m.	3 mg/kg	10 min predisbud
	Faulkner and Weary (2000)	Oral	3 mg/kg	2 h predisbud and 2 and 7 h postdisbud
	Milligan et al. (2004)	i.m.	3 mg/kg	10 min predisbud
Meloxicam	Allen et al. (2013)	Oral	1 mg/kg	12 h predisbud
	Allen et al. (2013)	Oral	1 mg/kg	At disbudding
	Heinrich et al. (2009)	i.m.	0.5 mg/kg	10 min predisbud
	Heinrich et al. (2010)	i.m.	0.5 mg/kg	10 min predisbud
	Mintline et al. (2013)	i.v.	0.5 mg/kg	55 min predisbud
	Stock (2015)	Oral	2.0 mg/kg	5 min predisbud

was included, and so on). Whereas these would likely be nondifferential within a study, it is possible some of these factors may interact with the effect of treatment, resulting in variability between effect magnitude or duration between studies. Depending on the nature of the disbudding insult, the delayed rise in cortisol may last a different length of time, which may account for some discrepancies in the 4 and 6 h meta-analyses. To fully explore any of these possible causes of heterogeneity, a larger number of studies would be required. Additionally, although care was taken to avoid errors in extracting data from graphs, this may have added to the observed heterogeneity between studies based on the resolution of the images available.

Effect of Local Anesthetic and NSAID Compared with Local Anesthetic Alone

Overall, beneficial effects were found at 3, 4, and 6 h postdisbudding when NSAID was given in addition to local anesthetic. This likely corresponds to the time after the duration of effect of the local anesthetic, and may be due to a reduction in inflammatory pain. Whereas a beneficial effect was seen at various time points for all classes of outcome (plasma cortisol concentration, pain behavior, and pressure sensitivity), these effects did not necessarily occur at the same time points for each outcome, and heterogeneity was substantial in some analyses, including several using pain behavior outcomes. The primary studies included in these meta-analyses vary between analyses (not all studies reported at all included time points), and therefore differences in time to effect by outcome may be a function of the outcome itself as well as study design, NSAID used, volume and route given, local anesthetic used, volume and route given, and specific characteristics of the different study populations. Similar to the findings in the comparison of local anesthetic to no treatment, sample sizes in many individual studies were quite small (ranging from 6 to 30 calves per group), which increased the chance for random variation in effect found between studies, although confidence intervals will also be wide. A lack of heterogeneity in many of the analyses pertaining to pressure sensitivity may reflect less inherent variability in this outcome compared with others, or it may be in part due to the similarity in study design and treatment, as most trials in these analyses were done by the same research group.

At 24 h, a protective effect of no treatment on plasma cortisol occurred, with moderate heterogeneity between studies. Other outcome measures at 24 h did not find this, and individual studies reporting at later time points did not see a continuation of this trend (Allen et al., 2013; Stock, 2015; Stock et al., 2016). It is possible unmeasured factors aside from treatment group contributed to this result.

Pain behavior was the most challenging of the outcomes to synthesize; not only did the studies measuring these outcomes potentially differ with regard to study design, specifics of treatment groups, and potential complications from extracting data from graphs, but also the duration of observation period differed between studies. The studies included in the pain behavior meta-analyses were the most varied in this respect, and this may be why overall effects were not consistent both within an analysis and between analyses for different outcomes at a similar time point. Overall, it is reasonable to conclude from our findings that some protective effect of NSAID use on pain behavior exists, and that this effect is seen after the duration of the effect of the local anesthetic and mitigates the delayed cortisol rise when no NSAID is given. However, based on the difficulties in combining studies in this area, it is not possible to estimate the exact nature of the effect nor its duration.

Clinical Relevance

The administration of local anesthetic was beneficial for reduction of the acute pain associated with cautery disbudding, with the caveat that a delayed rise in plasma cortisol occurred after the duration of effect of the local anesthetic. Administration of an NSAID in addition to local anesthetic showed benefits in the hours following the effect of the local anesthetic through reduced plasma cortisol, pain behaviors, and increased pressure sensitivity. Therefore, an NSAID and local anesthetic should be recommended over local anesthetic alone. However, the multitude of different NSAID, routes, dosages, and treatment intervals used in the studies included in the data synthesis likely contribute to much of the heterogeneity seen, driven in part driven by pharmacodynamics differences. The range of both different treatments and outcomes ordained an insufficient number of similar treatments measuring comparable outcomes to combine for subgroup analysis to explore what drove this heterogeneity. This precludes any overall conclusion on which specific NSAID treatment protocol resulted in the best outcomes.

Implications for Future Research

Both pressure sensitivity and pain behavior may be useful indicators of pain in the hours and days following disbudding; however, more standardization in study design, especially for pain behavior, would allow for

a greater ability to synthetize results from multiple studies. Whenever possible, total counts for entire time periods should be used to avoid potential bias due to random variation with short sampling intervals.

For all outcomes measured, reporting of numerical data in addition to figures are recommended (Sargeant et al., 2010). With online publication, supporting documents such as tables of all data collected (for example, in the case of outcomes with nonsignificant results the authors' do not, at the time, consider substantial) could be a requirement of the scientific journal to facilitate future data synthesis. The amount, quality, and combinability of data available from primary studies determines the ability to conduct a meta-analysis and influences the precision of the overall effect estimate.

Risk of bias assessment of studies included in our review was challenging, as much important information was often unreported. Studies that fail to report key design features, or those lacking sound methods, may result in biased effect estimates (Sargeant et al., 2010). Scientific journals that do not currently require authors and reviewers to follow reporting guidelines should reconsider their stance. For clinical trials in livestock species, use of The REFLECT Statement (O'Connor et al., 2010; Sargeant et al., 2010) could help better ensure quality information is available to end users.

CONCLUSIONS

Based on reductions in plasma cortisol, pain behaviors, and pressure sensitivity, we found that the use of local anesthetic and an NSAID is best practice for pain mitigation for cautery disbudding of calves 12 wk of age or less. The magnitude and duration of the effect of NSAID treatment was not possible to deduce from the literature, as much variation existed between studies. It is likely that differences in pharmacodynamic properties of the different NSAID treatments were responsible for much of the heterogeneity; however, there were not enough similar treatments measuring similar outcomes to conduct subgroup analysis to fully explore differences by treatments. This information would be useful to guide more specific veterinary recommendations, and we recommend consideration of more standardized outcome measurements in future research, especially for pain behaviors. In addition, adherence to reporting guidelines by authors would ensure more transparent and complete information available to end users.

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Appendix 32

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Addressing the pain associated with disbudding and dehorning in cattle

Kevin J. Stafford [a], David J. Mellor [b]

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Abstract

The pain caused by disbudding or dehorning of cattle and its alleviation may be assessed by behavioural, physiological and production responses. Disbudding can be carried out by cautery or the application of a chemical paste. Cautery disbudding and amputation dehorning stimulate definite pain related behaviours during and after the procedure but caustic disbudding causes little response during the procedure though it is followed by behaviours indicative of pain. All three procedures cause definite plasma cortisol responses but the response to amputation dehorning is significantly greater than the response to cautery or chemical disbudding. It has a characteristic format; a rapid increase following dehorning to a maximum concentration within 30 min, then a decline to plateau levels, followed by a return to pretreatment values at 7–8 h. Local anaesthesia administered before disbudding or dehorning eliminates pain-related behaviour and reduces the plasma cortisol response for about 1.5 h. Following amputation dehorning the plasma cortisol concentration then increases for about 6 h before returning to pretreatment levels. When local anaesthesia and a non-steroidal anti-inflammatory drug

(NSAID) are given before disbudding or dehorning the cortisol responses to these procedures are virtually eliminated. Chronic pain in the days following disbudding and dehorning is poorly understood. As a general rule, if pain relief is not available, cautery disbudding is preferable to chemical disbudding or amputation dehorning. If possible, local anaesthesia and better still local anaesthesia plus a NSAID should be used to minimise the pain caused by all three procedures.

Introduction

The prevention of horn growth (disbudding) or removal of horns (dehorning) are common practices on cattle farms (Stafford and Mellor, 2005) as cattle without horns are easier to manage and cause less injury, especially during transport (Marshall, 1977). In addition, hornless cattle require less trough space (Stookey and Goonewardene, 1996). Disbudding and dehorning are painful procedures and breeding polled, i.e. hornless cattle, eliminates the need to carry out these procedures. Some beef cattle breeds are polled but most dairy breeds and many beef breeds still grow horns. European type cattle (*Bos taurus*) have a simple genetic basis for polledness and could easily be bred as polled, but the genetic basis for polledness in humped cattle (*Bos indicus*) is more complicated and breeding for this phenotype is more difficult (Prayaga, 2007).

As disbudding or dehorning are standard practices on cattle properties a range of tools have been developed either to destroy or remove horn bud tissue (cautery, caustic paste, removal by knife) or cut off horns (saw, embryotomy wire, scoop, shears, electrical saw) (Sylvester et al., 1998a). Speed and safety for cattle and humans are important considerations during the procedure, as is managing the potential post-operative problems of haemorrhage, tissue necrosis, bone fracture, sinusitis and death (Weaver, 1986).

To prevent pain in cattle we can use general anaesthesia, local anaesthesia and/or systemic analgesia. General anaesthesia cannot easily be carried out on large numbers of cattle on farms. Local anaesthetics (usually lignocaine) and analgesic non-steroidal anti-inflammatory agents (NSAIDs) are the drugs used to minimise pain in cattle. The sedative xylazine also has some analgesic effects. At present using the first principles of veterinary analgesia, an analgesic protocol combining xylazine as a sedative/analgesic, local anaesthesia and systemic analgesia should alleviate or eliminate the pain caused by disbudding and dehorning. These drugs are available to veterinarians but may not be available to farmers for regulatory reasons or may be costly. Moreover, the observation

that disbudding by caustic paste or the rapid removal of small horns by scoop is not accompanied by pain-related behavioural responses has encouraged the use of these techniques without analgesia.

Setting definite ages for disbudding or dehorning is difficult as (1) the development of horns in some beef breeds occurs much later than in the dairy breeds and (2) some calves born in extensively managed herds are not handled until they are weaned at about 5–6 months of age when horn size makes amputation necessary. Dairy calves are managed intensively from birth and can be disbudded easily in the first few weeks of life. Some cattle are inadequately disbudded and need to have their horns removed by amputation at an older age. In some countries it is illegal to transport long horned cattle so that their horns are tipped before transport. This may or may not be painful depending on the length of horn tip which is cut off. Moreover, some organic farmers insist on leaving horns on cattle and consider the injuries inflicted by horns on other cattle acceptable. These injuries may be quite substantial skin tears. The primary author (KJS) has treated horses with serious abdominal injuries caused by the horns of cows with calves, and bulls.

Animals being disbudded or dehorned experience pain and behave accordingly by attempting to escape. Farmers and veterinarians, who undertake these procedures without analgesia or anaesthesia use restraint that allows the procedure to be carried out safely for the animal and themselves. Thus, they either carry out the procedure on young animals that are easily restrained manually, or restrain larger animals using ropes, head bails, crushes or sedation. The procedures themselves are usually simple, quick and easy.

Disbudding and dehorning without anaesthesia or analgesia cause pain but these practices also involve temporary isolation, restraint, and exposure to novel stimuli (close human contact, smells, blood) which may cause distress as shown by some physiological and behavioural responses. Differentiating between the distress and the pain caused by such procedures is difficult but effective local anaesthesia should eliminate the latter. Frequent and regular handling should reduce the stress caused by isolation and manual restraint and also help to differentiate between the two responses.

The pain caused by disbudding and dehorning and its alleviation has been the subject of research for about two decades and this paper reviews this work. The bulk of this research has been carried out on hand-reared dairy calves which may result in less stress during the process compared to the responses of single suckled beef calves. Pain and the efficacy of pain alleviation have been assessed using behaviour, physiological responses

and productivity. In addition, our understanding of the welfare significance of these procedures has been improved by our knowledge of the resultant pathology. Research has concentrated on the acute pain experienced during the procedure itself and in the hour following it, and the inflammatory pain experienced during the subsequent 12 h. Alleviation of these different forms of pain has also been studied. There is much less information on the pain experienced in the days and weeks following disbudding or dehorning. The paper will review the literature pertaining to the three major methods of horn removal, cautery disbudding, caustic disbudding and amputation dehorning. It will review behaviour and physiological studies in which the severity of the pain experienced by calves subjected to these procedures and the success of methods to alleviate this pain were assessed. It will conclude by looking at how this knowledge may be used to improve the welfare of calves in the future worldwide.

Section snippets

Cautery disbudding

Cautery disbudding is carried out on calves in the first 4–6 weeks of life. The horn bud and the horn generative tissue are destroyed by searing with a heated bar, usually one with a concave tip which heats the bud and surrounding tissue, for some seconds (Weaver, 1986). The bar may be heated electrically or by gas. During the process calves struggle violently and have to be restrained manually or in a head bail. The behaviours (rearing, falling down, pushing, head jerking and moving) are…

Chemical disbudding

During chemical disbudding a paste or a stick of sodium hydroxide or calcium hydroxide is used to destroy the horn bud (Weaver, 1986). These chemicals burn the tissues and this burn continues as long as the chemical is present. To minimise unnecessary skin damage, the area surrounding the horn should be defatted with surgical spirit. The bud may be scarified to make the caustic paste more effective. The caustic material may spread onto surrounding tissue especially following rain, be licked by…

Dehorning

Appendix 32

The acute pain caused by amputation dehorning is significant and animals will struggle to escape during the procedure. The plasma cortisol response of Friesian calves to this procedure has been described and appears similar in a number of trials. The total plasma concentration rises immediately, peaking after about 30 min, and it then decreases to a plateau which persists for 5–6 h before returning to pretreatment levels (Cooper et al., 1995, Petrie et al., 1996, McMeekan et al., 1997, McMeekan…

Comparison between methods

The cortisol response in the hours following cautery disbudding without anaesthesia or analgesia is lower than the response to chemical disbudding and amputation dehorning, which suggests that the former technique is less painful, acutely, than the latter techniques. The differences in the pathology caused by the three techniques probably explain the different cortisol responses. Cautery damages the skin around the horn buds with reasonable superficial injuries whereas amputation removes skin…

Implications and conclusions

Veterinary protocols and regulations for disbudding or dehorning calves vary between countries and usually reflect the availability of veterinarians, veterinary drugs and cattle management practices. In some countries it is now mandatory to provide pain relief during painful procedures. On some farms in the wealthy world, where veterinarians or veterinary technicians carry out the disbudding or dehorning, the cattle may be sedated, receive local anaesthesia and systemic analgesia, which will…

Conflict of Interest

We have no financial, personal or other relationships with people or organisations within three years of submitting this work that could inappropriately influence or be perceived to influence the work.…

Acknowledgements

We are grateful to Dr ACD Bayvel, Animal Welfare Directorate, Ministry of Agriculture and Forestry (MAF), for helpful discussion and to MAF Science Policy for financially contributing to the New Zealand-based studies referred to here.…

Appendix 32

Special issue articles Recommended articles

References (42)

K.E. Boandl *et al.*
Effect of handling administration of local anaesthetic and electrical dehorning on plasma cortisol in Holstein calves
Journal of Dairy Science (1989)

P.P. Faulkner *et al.*
Reducing pain after dehorning in calves
Journal of Dairy Science (2000)

B. Graf *et al.*
Behavioural and physiological responses of calves to dehorning by heat cauterisation with or without local anaesthesia
Applied Animal Behaviour Science (1999)

C. Grondahl-Nielsen *et al.*
Behavioural, endocrine and cardiac responses in young calves undergoing dehorning without and with use of sedation and analgesia
The Veterinary Journal (1999)

A. Heinrich *et al.*
The impact of meloxicam on postsurgical stress associated with cautery dehorning
Journal of Dairy Science (2009)

D.O. Kihurani *et al.*
Healing of dehorning wounds
British Veterinary Journal (1989)

S.A. Laden *et al.*
Effects of stress from electrical dehorning on feed intake, growth and blood constituents of Holstein heifer calves

Appendix 32

Journal of Dairy Science (1985)

C.M. McMeekan *et al.*

Effects of regional analgesia and/or a non-steroidal anti-inflammatory analgesic on the acute cortisol response to dehorning in calves

Research in Veterinary Science (1998)

J.P. Morisse *et al.*

Effect of dehorning on behaviour and plasma cortisol responses in young calves

Applied Animal Behaviour Science (1995)

M. Stewart *et al.*

Eye temperature and heart rate variability of claves disbudded with or without local anaesthetic

Physiology and Behaviour (2008)

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Can a social partner alleviate conditioned place aversion caused by isolation and pain in dairy calves?

2023, Applied Animal Behaviour Science

Show abstract

Wound healing and pain sensitivity following caustic paste disbudding in dairy calves

2023, Journal of Dairy Science

Show abstract

Cortisol and pain-related behavior in hot-iron disbudded goat kids sedated with xylazine and locally infiltrated with lidocaine

2023, Journal of Veterinary Behavior

Appendix 32

Show abstract

Dairy vs beef production – expert views on welfare of cattle in common food production systems

2022, Animal

Show abstract

Graduate Student Literature Review: Role of pain mitigation on the welfare of dairy calves undergoing disbudding

2022, Journal of Dairy Science

> *Citation Excerpt :*
>
> ...Disbudding is the removal of the horn-forming tissue before its attachment to the skull, whereas dehorning is the removal of the horn after this occurs, typically at 2 to 3 mo of age (CVMA, 2016). Disbudding is recommended over dehorning, because it is less invasive and less painful (Stafford and Mellor, 2005, 2011). Horned dairy cattle demonstrate a higher proportion of agonistic behaviors without body contact (such as a cow retreating from the horned cow without any body contact necessary) as well as more aggressive behaviors compared with dehorned cattle (Lutz et al., 2019)....

Show abstract

Comparison of alternative methods for thermal disbudding in calves

2022, Journal of Veterinary Behavior

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Appendix 32

J. Dairy Sci. 105:6220–6239
https://doi.org/10.3168/jds.2021-21552

Effect of plane of nutrition and analgesic drug treatment on wound healing and pain following cautery disbudding in preweaning dairy calves

Cassandra N. Reedman,[1]* Todd F. Duffield,[1] Trevor J. DeVries,[2] Kerry D. Lissemore,[1] Sarah J. J. Adcock,[3] Cassandra B. Tucker,[4] Sarah D. Parsons,[2] and Charlotte B. Winder[1]
[1]Department of Population Medicine, University of Guelph, Guelph, Ontario, N1G 2W1 Canada
[2]Department of Animal Biosciences, University of Guelph, Guelph, Ontario, N1G 2W1 Canada
[3]Department of Animal and Dairy Sciences, University of Wisconsin, Madison 53706
[4]Center for Animal Welfare, Department of Animal Science, University of California, Davis 95616

ABSTRACT

The objective of this study was to determine the effect of a biologically normal plane of nutrition compared with a limited plane on the primary outcome wound healing, and one dose of nonsteroidal anti-inflammatory drug (NSAID) compared with 2 on the secondary outcomes: lying behavior, haptoglobin concentrations, and mechanical nociceptive threshold (MNT) in calves disbudded via cautery iron. Eighty female Holstein calves were enrolled at birth, individually housed, and fed via a Calf Rail system (Förster Technik). A 2 × 2 factorial design was used to assess the effect of plane of nutrition and an additional NSAID. Calves were randomly assigned to a biologically normal plane of nutrition (BN; offered up to 15 L/d) or a limited plane (LP; offered up to 6 L/d) and to receive one or 2 doses of meloxicam. All calves received a lidocaine cornual nerve block and a subcutaneous injection of meloxicam 15 min before cautery disbudding at 18 to 25 d of age, and half the calves received an additional injection of meloxicam (0.5 mg/kg) 3 d after disbudding. Tissue type present, wound diameter, and wound depth were evaluated 2 times per week for 7 to 8 wk as measures of wound healing, lying behavior was recorded beginning 1 to 2 wk before disbudding until 7 to 8 wk after as a behavioral indicator of pain, haptoglobin concentrations were measured once per day for 7 d after disbudding, and MNT was evaluated 2 times/wk for 3 wk. Survival analyses were analyzed using Cox regression models (wound healing) and continuous data were analyzed using mixed-effect linear regression models. Only 12% of horn buds were completely healed by 7 to 8 wk after disbudding and 54% had re-epithelized at this time. At any time, wounds from BN calves were more likely to have had re-epithelization occur compared with wounds from LP calves (hazard ratio: 1.93, 95% CI: 1.18–3.14). Wounds from calves that received only one dose of NSAID were more likely to have re-epithelization occur, compared with wounds from calves given 2 doses (hazard ratio: 1.87, 95% CI: 1.15–3.05). Wounds from BN calves had smaller diameters and depths over time beginning on wk 3 compared with LP calves. Wounds from calves that received an additional NSAID had larger diameters and depths over time beginning on wk 4 and 3 respectively, compared with calves that only received one dose of NSAID. Calves that received an extra NSAID tended to be less sensitive 7, 10, and 17 d after disbudding compared with calves that only received one dose and spent less time lying in the week after disbudding. Calves on the BN milk program were more active compared with LP calves with lower lying times, fewer lying bouts per day, and longer average lying bouts. Our results indicate that a BN milk feeding program for calves can result in faster healing times and more activity, and that providing an extra NSAID 3 d after disbudding appears to slow the healing process but may result in less pain experienced by the calf 1 to 2 wk after the procedure. This study is also among the first to demonstrate that after the complete removal of the horn bud, wounds can take more than 8 weeks to re-epithelize and fully heal.

Key words: nonsteroidal anti-inflammatory drug, calf, dairy, analgesia

INTRODUCTION

Disbudding is a common procedure in the dairy industry (USDA, 2018; Winder et al., 2016). Although it is clear it is a painful procedure (Stock et al., 2013), especially when performed without anesthesia or analgesia (Calderón-Amor and Gallo, 2020), it is unclear how long this pain persists. Although many individuals perceive disbudding to be a painful procedure (Hoe and

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*Corresponding author: creedman@uoguelph.ca

Ruegg, 2006; Hokkanen et al., 2015) and are in favor of the use of pain control (Kling-Eveillard et al., 2015) believing it to be effective (Robbins et al., 2015), full adoption of pain control use in the United States and Canada has not been reached. In the United States, only 28% of dairy operations reported use any form of pain control (anesthetics or analgesics) for disbudding procedures (USDA, 2018), whereas in Canada, 66 and 25% of cautery users report using local anesthetics and analgesics, respectively (Winder et al., 2018).

The provision of a local anesthetic and a nonsteroidal anti-inflammatory drug (**NSAID**) substantially reduces pain-related outcomes for both cautery (Faulkner and Weary, 2000; Heinrich et al., 2010; Winder et al., 2018) and caustic paste disbudding (Stilwell et al., 2009; Winder et al., 2017; Reedman et al., 2020). Haptoglobin is an acute phase protein and an indicator of inflammation in cattle that has been reported to increase in response to disbudding (Allen et al., 2013; Glynn et al., 2013). Calves provided with both a local anesthetic and an NSAID for disbudding procedures have been reported to have decreased haptoglobin concentrations compared with calves receiving less or no pain control (Ballou et al., 2013; Erdogan et al., 2019; Reedman et al., 2020). Stressful or painful events such as disbudding have also been reported to affect the lying behavior of calves (Molony and Kent, 1997; Black et al., 2017; Sutherland et al., 2018a), including (in the 4 h after disbudding) spending less time lying (Sutherland et al., 2019) and being more restless (moving from standing to lying frequently) (Sutherland et al., 2018b). Some of these negative responses can be mitigated with the use of a local anesthetic and NSAID (Sutherland et al., 2018a).

Most previous studies have only evaluated calves on the day of disbudding or up to 4 d or 3 wk after (Theurer et al., 2012; Huebner et al., 2017; Sutherland et al., 2019). More recently, researchers have reported that wound re-epithelialization after disbudding can range between animals from 42 to 91 d and 40 to 70 d in calves after disbudding (Adcock and Tucker, 2018; Adcock et al., 2019, respectively), and 35 to 63 d in goat kids after disbudding (Alvarez et al., 2019). These researchers (Adcock and Tucker, 2018; Adcock et al., 2019; Alvarez et al., 2019) evaluated the length of time for wounds to form new epithelium, rather than the time it took for wounds to completely contract. During this time, the tissue around the horn bud is more sensitive for up to 105 d after disbudding compared with control animals (Casoni et al., 2019) and is more sensitive [lower mechanical nociceptive threshold (**MNT**)] compared with new epithelium formed on the wound for this entire healing process (Adcock and Tucker, 2018). Calves administered lidocaine 11 d after cautery disbudding exhibit behavioral changes consistent with experiencing ongoing pain (Adcock et al., 2020). Additionally, although sham disbudded calves find the provision of lidocaine to be a painful experience and will avoid it, disbudded calves will choose to receive an injection of lidocaine at 20 d after disbudding, indicating that they are still in pain at this point and will trade off the short-term pain of the lidocaine with the longer-term pain relief (Adcock and Tucker, 2020).

Nutrition has been reported to be a crucial part of the wound healing process in humans as malnutrition (encompasses poor nutritional intake to overall metabolic equilibrium) has been well documented to impede wound healing (Williams and Barbul, 2003; Stechmiller, 2010; Wild et al., 2010); however, this has not been evaluated in disbudding wounds in calves. Although it is becoming more common to feed an increased nutritional plane to young dairy calves, 33% of Canadian producers are still feeding calves low levels of milk (<6 L/d; Winder et al., 2018). When calves are offered milk ad libitum, they will drink between 10 to 12 L/d on average (>20% of BW by volume; Khan et al., 2011), and researchers have reported that calves fed 6 L of milk daily display signs of hunger (Rosenberger et al., 2017). There are many benefits to feeding an increased nutritional plane to young dairy calves including improving calf health and performance (Todd et al., 2017) and improved first lactation milk production (Gelsinger et al., 2016). Taken together, it is known that the plane of nutrition has long-term biological effects in calves, specifically, and in the context of wound healing in other species. It seems plausible that plane of nutrition, therefore, is worth exploring in the context of the large amount of variation in time taken for disbudding wounds to re-epithelialize (Adcock and Tucker, 2018; Adcock et al., 2019; Alvarez et al., 2019).

Therefore, the objectives of this study were to assess the effect of a biologically normal plane of nutrition (**BN**; up to 15 L/d) or limited plane (**LP**; up to 6 L/d) on wound healing after disbudding in dairy calves, as well as the effect of an additional dose of meloxicam 3 d after disbudding on pain and inflammation (haptoglobin). We predicted that BN calves would have improved wound healing, smaller wound diameters and depths over time compared with LP calves. We also predicted that calves receiving an additional dose of NSAID would have lower haptoglobin concentrations, decreased MNT, and improved lying behavior outcomes compared with calves only receiving one dose.

MATERIALS AND METHODS

This manuscript is reported according to guidelines for randomized controlled trials in livestock and food

safety (O'Connor, 2010). An a priori trial protocol was published to the University of Guelph Institutional Repository on August 20, 2019, and is available at: http://hdl.handle.net/10214/17494.

Animal Use

This trial was conducted between October 2019 and November 2020 (with enrollment temporarily halted from March to June 2020 due to the COVID-19 pandemic) at the Ontario Dairy Research Centre in Elora, Ontario, Canada. Use of animals and all methods for this study were approved by the University of Guelph Animal Care Committee (AUP#4268) in compliance with animal use guidelines of the Canadian Council on Animal Care (2009).

Housing and Management

Calf navels were dipped in 2.5% iodine solution immediately following birth, and once more during the next day of life. All calves were administered one oral 3-mL dose of a Rota-Coronavirus vaccine (Calf-Guard, Zoetis) at least 30 min before receiving colostrum, and 1.5 mL of vitamin E and selenium subcutaneously on the first day of life (Dystosel; Zoetis; Selon-E; Vetoquinol). After the first colostrum feeding, and once every 24 h for the first 7 d of life, all calves were administered halofuginone lactate (Halocur, Merck Animal Health; 2 mL/10 kg) for reduction of *Cryptosporidium parvum*. All calves were vaccinated with 1 mL of an intranasal respiratory vaccine at d 42 to 63 for the prevention of bovine respiratory disease (Inforce-3 intranasal spray; Zoetis Inc.).

Within 2 h of birth, calves were moved from the calving pens to the calf nurseries and were placed in individual pens inside one of 4 nursery rooms; each room had 11 individual pens. Calves were housed in these individual pens (152 × 167 cm) for the entirety of this trial. These pens were bedded with wood shavings, with new bedding added daily and completely replaced every 4 d. All 4 sides of the individual pens were vertical steel bars, so calves had both visual and auditory contact with all other calves in the same room and limited physical contact with neighboring calves.

Nutrition

Calves were fed 3 L of colostrum within the first 2 h of life (and 30 min after administration of the oral vaccine) offered first in a bottle, but tube fed via an esophageal tube feeder if necessary. Another 3 L of colostrum were offered 6 to 12 h after the first feeding. Colostrum quality was measured using a refractometer and was required to be at a minimum Brix value of 22% (Calf Lab refractometer; Golden Calf Company LLC). For the second feeding on the first day of life and the 3 feedings on the second day of life, calves were fed transition cow milk (milk from the second to sixth milkings from fresh cows) by bottle in 2-L quantities. Until calves were fully weaned at d 63, they were fed using a Calf Rail system (Förster Technik) that ran 5 times daily at 0500, 0900, 1300, 1700, and 2100 h. Beginning on their third day of life, calves were fed an acidified milk replacer at a concentration of 150 g/L (5.4 pH, 26% CP, 18% crude fat; BioForce Acidified Milk Replacer, Grand Valley Fortifiers) by the Calf Rail system. Depending on the calf's milk treatment group, they were offered either 3 L (BN) or 1.2 L (LP) of milk replacer each time the Calf Rail ran. Calves were trained (assisted if needed) at every feeding until they could reliably get up on their own to drink their allotted milk. Barn staff checked daily at 1730 h for calves that had not consumed 4 L of milk since the first feeding of the day; these calves were bottle fed milk replacer until they had drunk at least 4 L for the entire day with the option to drink more milk at their last feeding at 2100 h as well. All additional bottle feedings were recorded and used to determine the total daily milk consumption of each individual calf. Further information on the Calf Rail system and calves' nutrition protocol is reported in Parsons et al. (2022).

Calves had access to water in an 8 L bucket attached to the back of their pen 24/7 from birth and were offered a solid starter diet in an 8 L bucket attached to the back of their pen beginning at d 5 of life. Calves on this trial were a part of a nutrition trial being conducted in collaboration with another research group at the same time as the present trial, examining the effect of a novel milk by-product-based starter diet compared with a grain-based starter diet (AUP#3722; Parsons et al., 2022).

Both milk treatment groups were weaned using a gradual weaning program. The Calf Rail automatically gradually decreased the calves' allotted milk in equal increments beginning on d 43 until d 63 and on d 64 all calves no longer received any milk. Calves remained on this trial after weaning in their individual pens until d 77 of life, and on d 78 they were moved to group heifer housing and were no longer followed by the researchers.

Enrollment

All heifer calves born were eligible and enrolled onto the trial. Calves were health scored by researchers using the Calf Health Scorer App (McGuirk, 2013; McGuirk

and Peek, 2014) twice weekly beginning at d 2 of life. Any calf that was appreciably polled by palpation of the horn bud at the time of disbudding was excluded from the trial. Calves defined as ill (any one of: 3 fecal consistency and rectal temperature; ≥2 for all other health parameters) on the day of disbudding were not disbudded but could be included the following week if healthy at that time. Calves defined as ill both on their original disbudding date and one week later were excluded from the trial.

Treatment Groups

This was a 2 × 2 factorial design study that consisted of 2 separate variables of interest (milk feeding level and second dose of NSAID) with 2 treatment groups within each variable. Within each milk treatment group, there were an equal number of calves assigned to the 2 NSAID treatment groups to make up 4 treatment groups (BN and control; BN and additional NSAID; LP and control; LP and additional NSAID). Calves on the BN treatment were offered up to 15 L/d of milk, split into 5 feeding of 3 L each feeding from d 2 to 42, and LP calves were offered up to 6 L/d of milk split into 5 feedings of 1.2 L each feeding from d 2 to 42. All calves received one dose of meloxicam before disbudding, with half receiving a second dose 3 d after disbudding. Calves were disbudded when they were between 18 and 30 d of age. Treatment groups were all balanced to ensure an equal number of calves per room in both milk and NSAID treatments, while also accounting for the 2 additional starter feed treatments, which included in the collaborating nutrition trial feeding (1) only a mixture of 95% grain-based starter pellet (20% CP, Bionic Calf Grower Pellet, Grand Valley Fortifiers) and 5% wheat straw, and (2) 150 g/d (as-fed) of a whey-based starter (LifeLaunch 4C; Grand Valley Fortifiers), with the grain-straw mix also provided once calves consumed the entire 150 g/d on 2 out of 3 consecutive days. From the previously mentioned treatment groups, an equal number of calves within each of those 4 groups was assigned to each of the starter diets to balance for these as well.

Before all baseline MNT measurements being taken, the hair around the horn buds was clipped. Fifteen minutes before disbudding, all calves received a lidocaine cornual nerve block (6 mL per side, lidocaine hydrochloride injection 20 mg/mL, Bimeda-MTC Animal Health Inc.) and a subcutaneous injection (in the neck) of 0.5 mg/kg meloxicam (Metacam 20 mg/mL Solution for Injection, Boehringer Ingelheim). Cornual nerve block technique was performed as described in Winder et al. (2017) by insertion of an 18-gauge, 1.5-inch needle caudal to the eye, ventral to the temporal ridge, injecting 6 mL per side fanned out in multiple directions. Calves in the extra NSAID group received their second dose 72 h after disbudding as described above.

To assess the efficacy of the nerve block, MNT was assessed immediately before disbudding, any calf that was not adequately desensitized (MNT value of 10 kilograms of force at all 8 locations) was administered an additional 2 mL of lidocaine on the appropriate side. Disbudding was performed by CNR (author) for the entirety of the trial. The horn bud was removed completely from the calf and will be referred to as a "bud-out" technique. The cautery iron (Express Pistol-Grip Dehorner, The Coburn Company, Inc.) was preheated for at least 3 min until it reached a temperature of approximately 650°C. The iron was then applied only once to each horn bud (always beginning with the left) until a copper ring was observed and horn buds were removed by maneuvering the iron in a circular motion in on itself until all horn bud tissue was fully removed, as described in Reedman et al. (2021).

Primary Outcome and Data Collection

The research team attended farm on Tuesdays and Fridays to collect measurements for this trial. Disbudding always occurred on a Tuesday and all calves that were eligible (18 to 25 d of age and considered healthy as previously described upon initial assessment, but eligible up to 30 d of age if the calf was too sick on their original disbudding day) on that day were disbudded. After disbudding measurements for MNT and wound assessments were taken at the same time with MNT measurements collected first, followed by wound measurements, and finally photos of the wounds were taken last.

Wound Assessments

Wound diameter and depth were measured by the same researcher for the entire trial. These measurements were collected using a digital caliper, in mm (Mastercraft Digital Caliper, 6 in). The scoring system for tissue type during wound healing is described in Figure 1. The diameter measurements were taken at the widest part of each wound and were collected until there was no longer any crust or granulation tissue present, only new epithelium. Depth measurements were collected using the depth rod function on the caliper. Depth was measured at the deepest part of each wound and was collected until the necrotic tissue had fully detached from the skull of the calf and there was no longer depth measurable on the wound. If there was pu-

rulent discharge in the wound, the depth of the wound was not measured. Wound measurements were collected directly after disbudding and every Tuesday and Friday until the calves left the calf room (when they were 78 d of age). Therefore, depending on the age of the calf on the day of disbudding, measurements were collected at +3, +7, +10, +14, +17, +21, +24, +28, +31, +35, +38, +42, +45, +49, and +52 d relative to disbudding with some calves being followed up to +56 and +59 d after disbudding if they were disbudded earlier in the eligible window.

Wound Healing

Photos of the disbudding wounds were taken by the same researcher for the entirety of the trial. Following the protocol described by Adcock and Tucker (2018), photos were taken using an iPhone XR (Apple Inc.) to meet the following criteria for the wound: centered in the frame, in full view (taken straight on, not at an angle), clear, sharp and in focus, lighting was uniform (always taken in the calf nursery, no shadows), only the immediate area surrounding the wound was in

Example	Tissue	Description
Wound characterization on day of disbudding		
	Bone or fat	Smooth, white surface, may have pink tinge, and/or yellow ridged tissue
Healing process (scored d 1 or later)		
	Attached necrotic tissue	Yellow or white centre (likely sequestrum or fat) surrounded with dried black exudate that is below the plan of undamaged tissue; dried exudate may obscure yellow centre; none of the wound edge has lifted away from scalp
	Detaching necrotic tissue	The outside edge of the ring around the wound has started to lift away from scalp
	Pus/purulent discharge	Thick, fresh, exudate that is cloudy with a pink or gray tinge
	Granulation	Light red/dark pink, opaque, bumpy tissue; only scored once necrotic tissue begins to detach
	Crust	Rough tan, dark red or black dried exudate that is at or above the plane of undamaged tissue
	Epithelium	Layer of translucent skin is present; other tissue types or blood are absent
	Healed/fully contracted	Wound is fully contracted; scar line may be visible; other tissue types or exudate are absent

Figure 1. The scoring system used for evaluating tissue types in disbudding wounds.

frame (no open space, ear, or eye), and skin was not folded around the wound. Photos of each wound were taken directly after disbudding and following the same schedule as the wound measurements. Photos were taken directly after measurements. Once the trial was complete, a third-party observer, blind to treatment groups, was trained to score the wound photos based on the presence or absence of the tissue types described in Figure 1. This chart was developed based on the scoring system described in Adcock and Tucker (2018), but modified by SJJA and CBT for bud-out disbudding. An interobserver reliability score was calculated for each tissue type based on this observer's scoring of 300 photos (9 calves from the day of disbudding to the end of their follow-up) from the training module by SJJA and CBT. A cut-off of 0.8 was used for assessing the kappa statistic (considered very good agreement). Once the third-party observer was trained, they scored all of the photos (2,534) and recorded the data into Microsoft Excel (Version 16.5, Microsoft Corp.).

Secondary Outcomes and Data Collection

Standing and Lying Behavior. Standing and lying behavior were measured using HOBO Pendant G Data Loggers (Onset Computer Corp.) attached horizontally to the rear right leg of each calf using a cohesive bandage and set to record the tilt of the x-, y-, and z-axis every 60 s, as described by Bonk et al. (2013). The y-tilt was used to evaluate when the calves were lying down versus standing. Data were downloaded using HOBOware Pro Software (Onset Computer Corp.), imported into Microsoft Excel (version 16.6, Microsoft Corp.), and categorized into 3 outcomes: average daily lying time, average daily lying bout length, and number of lying bouts in a day. Each day that the loggers collected data for began at 0000 h and ended at 1159 h. The HOBO sensors were attached to the calves when they were 11 d of age (1–2 wk before disbudding) and collected data until the calves completed the trial (77 d of age). The data collected in the 7 d before disbudding were used as baseline values for average daily lying time, average daily lying bout length, and number of lying bouts in a day. Data from the loggers were downloaded every week after attachment with new loggers attached each week. The exact time that HOBO loggers were switched for each individual calf was recorded in Microsoft Excel (Microsoft Corp., Redmond, WA) and was used to splice together all 8 to 9 wk of lying behavior data into one file per calf. If data collected by the loggers was incorrect upon visual inspection and was able to be corrected (such as the logger flipping upside down while collecting data), this was accomplished by adjusting the data however necessary (eg., for an upside down logger the data were adjusted by 180°).

Serum Haptoglobin. Haptoglobin was collected to evaluate inflammation after the disbudding procedure. Blood samples were collected using red top vacutainer tubes by venipuncture of the jugular vein. Baseline values for this outcome were collected at −60 min relative to disbudding. Further samples for this outcome were collected at +4 h and daily for 7 d after the disbudding procedure. The haptoglobin sample on d 3 was collected in the afternoon 4 h after the second dose of the NSAID was administered to calves assigned to that treatment group. As soon as possible after collection and once samples had clotted, samples were centrifuged for 15 min at 2,000 × *g* on farm. Serum from each sample was separated, collected, and stored at −20°C until the time of testing. All samples from trial were run as one batch at the Animal Health Laboratory at the Ontario Veterinary College (Guelph, Ontario, Canada) on a Roche Cobas 6000 c501 biochemistry analyzer (Hoffmann-La Roche Ltd.) using a methemoglobin stock reagent with formulas and operating conditions developed by J.G. Skinner Laboratory, Veterinary Investigation Centre (Aberdeen, Scotland; Makimura and Suzuki, 1982; Skinner et al., 1991). Methemoglobin binds with haptoglobin to form a stable methemoglobin-haptoglobin complex. Measurement of haptoglobin was based on the peroxidase activity of this complex in acidic conditions. A hydrogen peroxide and guiacaol solution served as the substrate for the reaction and color development was read at 480 nm wavelength. The instrument was calibrated using standards and controls before running the samples. The interassay coefficient of variation was 5.2%.

Mechanical Nociceptive Threshold. The MNT was measured using a pressure force algometer (Force Ten FDX Compact Digital Force Gage, Wagner Instruments), following the protocol described by Reedman et al. (2021). One researcher collected all MNT measurements for the entire trial, for further information on MNT training and inter- and intra-observer reliability (see Reedman et al., 2020). The algometer was equipped with a rubber tip (approximately 1 cm in diameter) and measurements were taken at 4 locations around each horn bud in the same order (based on the numerical order in Figure 2) always beginning with the left horn bud (Figure 2). Calves were restrained using a halter tied to the side of their pen; the algometer was initially placed lightly on the site until the calf was motionless and then force was applied slowly until there was a withdrawal or pain response from the calf; note that rate of pressure application was not formally measured or controlled. These responses included the

calf jerking or shaking their head, pulling back sharply, or jumping up or forward. The sensitivity of the area was measured in kilograms of force (**kgf**) applied to each location and was referred to as the MNT. The MNT values at the 4 locations on each horn bud (8 locations in total) were averaged to calculate one value for each calf at each time point. Minimum values were recorded at 0.5 kgf and maximum values at 10 kgf. The first MNT measurements were collected 60 min before disbudding to acclimate the calf to the test, and then baseline values were collected from each calf 30 min before the procedure. Directly before disbudding (15 min after nerve block administration), MNT measurements were taken to determine whether the nerve block was successful at desensitizing the animal (the calf showed no response to the maximum value of 10 kgf at all 8 locations). Follow-up measurements were collected 4 h after disbudding and then on the same days as the wound measurements and photos for 3 wk after disbudding. These measurements were the first collected every day to attempt to eliminate any type of annoyance response to this test by the calf due to over handling.

Sample Size. Our initial trial protocol included a sample size considering wound diameter as the primary outcome based on an expected difference of 2 mm with a standard deviation of 4 mm for the milk treatment groups, with 95% confidence and 80% power and was adjusted for mild clustering by day (average n sampled per cluster = 3, intraclass correlation coefficient = 0.02). The calculated sample size was 60 calves per milk treatment group for a total of 120 calves. In March 2020, the trial was halted due to the COVID-19 global pandemic and resumed in June 2020. During this time a blinded interim analysis was conducted using data from the calves that had completed the trial by March 2020 (n = 26 calves total). Based on this, the difference in wound diameter between treatment groups of one variable of interest (BN and LP calves; unknown by the researcher which treatment group was which at the time of analysis) was 5 mm (5.3 mm and 10.3 m) with a standard deviation of 6 mm. As a result, we reduced our sample size to a total of 40 calves in each milk treatment group, for a total of 80 calves.

Figure 2. Figure from Reedman et al. (2021) of locations around the horn buds measured using a pressure force algometer numbered in the order which they were measured. Measurements were always taken beginning with the left side of every calf. Illustration created by Shelby Nielson.

Treatment Allocation and Blinding. A random pattern of treatments was created using a random number generator in Microsoft Excel (Microsoft Corp.) and was repeated until 80 calves had been enrolled onto the trial. Treatments were assigned based on the next available pen that a new calf was to be placed into. The pattern of treatments was correlated with available pens, following the same flow of pens as a room filled up (a total of 11 individual pens per room). For example, treatments were A, B, C, D, and were allocated in the pattern D, B, A, C. Treatment D was assigned to the first pen in room 1, pen 2 was assigned to treatment B, pen 3 to treatment A, pen 4 to treatment C, pen 5 to treatment D, and so on. As a calf was born, she was placed in the next available pen and assigned to the corresponding treatment group associated with that pen. This randomization protocol controlled for the effect of the calves' assigned pen location within a nursery room. CNR performed all data collection and disbudding was blinded to the treatments that calves were assigned to. This researcher administered the primary dose of the NSAID as well as the lidocaine cornual nerve block. A separate researcher (SDP), who was not involved in any evaluation of outcomes or analysis, was not blinded to the treatment groups and administered the second dose of the NSAID. This researcher also assigned calves to their appropriate treatment group and measured their milk consumption. Caretakers on the farm were blind to the NSAID groups but were aware of the milk treatment group for the calves. Once statistical analysis was completed by the blinded researcher, treatment allocation was revealed for interpretation of the results.

Statistical Analysis

All recorded data were entered into Microsoft Excel (Microsoft Corp.) and imported into STATA15 (Stata/

IC Version 15.1 for Mac, StataCorp). Descriptive statistics were reviewed for all variables. Continuous variables (wound diameter, wound depth, MNT, serum haptoglobin, time spent lying, number of lying bouts, and average lying bout length) were also assessed for normality, linearity, and variation through assessment of outliers and residuals. Model fit was evaluated through the assessment of normality and variation of standardized residuals and normality of the BLUP. Based on the level of variation between wounds of the same calf, the experimental unit for analyses of wound diameter and depth, and wound healing outcomes was the horn bud. For analyses of daily lying time, number of lying bouts, average lying bout length, haptoglobin, and MNT, the calf was the experimental unit. Wound healing was also assessed at the calf level based on both wounds within a calf reaching a stage of healing. This outcome was evaluated based on the length of time in days that it took for individual wounds and both wounds within one calf to reach both the epithelium and healed (Figure 1) stages of healing, as well as the binary result of whether a calf had both wounds reach these 2 stages by the end of follow-up (1) or not (0). These data were also used to assess the length of time that different tissue types were present for during the healing process. Results were considered significant if the P-value was ≤ 0.05 and were considered to have a tendency to be significant if the P-value was >0.05 but <0.1.

All outcomes included repeated measures; therefore, mixed-effect regression models were built. The Kenward-Roger method was used to approximate denominator degrees of freedom and F statistics for all mixed-effect regression models; coefficients in the model and P-values did not change with the use of this approximation. Baseline values were included as a fixed effect in the model to control for differences between calves before disbudding for appropriate outcomes (haptoglobin, MNT, daily lying time after disbudding, number of lying bouts after disbudding, and average lying bout length after disbudding). Milk and NSAID treatment were kept in as fixed effects for every model built and interactions were always tested between these 2 variables. If no interaction was detected between milk and NSAID treatment it was not further reported, and data were reported separately for each variable. For continuous, normally distributed data (wound diameter and depth, MNT, serum haptoglobin, daily lying time, number of lying bouts, and average lying bout duration) linear models were used, for binary data [healing end point (epithelium and healed)] logistic models were used, and for survival analyses data (time to re-epithelization and time to healed) Cox proportional hazard models were used. When wound was the experimental unit for linear models (wound diameter and depth) random effects were included for wound side nested within calf nested within calf room nested within day of disbudding. When wound side was the experimental unit for survival analyses (wound healing), calf was included as the shared frailty effect and disbudding date was included as a fixed effect. When calf was the experimental unit for linear models (daily lying time, number of lying bouts, average lying bout duration, haptoglobin, and MNT), random effects were included for calf nested within calf room nested within disbudding date. Last, when calf was the experimental unit for survival analyses (both wounds within one calf healing), disbudding date was included as the shared frailty effect. Calf age on the day of disbudding was offered to each multivariable model and kept if significant. Starter diet treatment (grain or whey-based pellet) from the collaborating study was offered to every statistical model and was also tested for interaction effects with both the milk and NSAID treatment as well as with the time variable in each model and was kept if significant or if it was found to be a confounder ($>20\%$ change in other coefficients in the model with the removal of this variable) to control for these effects. All variables were evaluated for potential collinearity and correlation issues.

For all models built, univariable models were built first to assess the statistical significance of independent variables using a liberal P-value of 0.2. Variables were then offered to the multivariable model to further assess significance using a P-value of 0.05 and tendencies at >0.05 but <0.1. For all linear models (wound diameter, wound depth, MNT, haptoglobin, daily lying time, number of lying bouts, and average lying bout length), continuous independent variables (age on the day of disbudding and time since disbudding) were assessed for linearity with the dependent variable. If an independent variable was detected to have a nonlinear relationship with the dependent variable (time since disbudding) it was categorized. First order interaction terms were assessed between milk treatment, NSAID treatment, starter treatment, and time since disbudding for all models and were kept if statistically significant. For wound diameter and depth models, time was modeled in weeks since disbudding. Before the removal of any variable from the multivariable model for each outcome, each variable was assessed statistically for confounding effects on other variables in the model. If a variable was found to be a confounder (as previously described), it was kept in the model.

Wound healing outcomes were assessed at the level of the horn bud as well as at the calf (both wounds in one calf reaching the healed or epithelium stage). Regardless of the experimental unit, hazard ratios (**HR**)

for treatment groups were evaluated from Cox proportional hazard models. Kaplan-Meier failure curves were also constructed to visually compare differences in healing time between treatment groups while controlling for the other treatment not being assessed (i.e., if comparing milk treatments, the curve controlled for the effects of the NSAID treatment as well). When evaluated at the horn bud level, the length of time it took for individual wounds to reach the end points (epithelium or healed) was modeled based on the first day these tissue types were present for. For evaluation at the calf level, the length of time it took for both wounds in an individual calf to reach the end points (epithelium or healed) was modeled. The presence of pus or purulent discharge was evaluated and noted in the wound photos as well.

In the lying behavior models (daily lying time, number of lying bouts, and average lying bout length) an individual model was built for each outcome. Because milk treatment differences were detectable and present before disbudding, all the lying behavior models evaluating milk treatment were built using the entire time period that lying behavior was collected for (d 11 of age to d 77 of age). However, because NSAID treatment was only given 3 d after disbudding, differences were not detectable across the entire 66 d that data were collected for. Due to biological plausibility, lying behavior models (daily lying time, number of lying bouts, and average lying bout length) evaluating NSAID treatment were built to assess differences in the week after disbudding while controlling for baseline values the week before disbudding and controlling for differences attributable to the milk treatment.

RESULTS

In total, 95 calves were enrolled in this study, with 80 calves completing the trial. Two calves were excluded because they were polled, 2 were euthanized during the study due to severe respiratory disease and injury, 2 were excluded because they were disbudded with a different cautery iron, one was excluded because it was sick on the day of disbudding and a week later, and 8 were excluded because they were lost to follow-up due to the COVID-19 pandemic. Of the 80 calves, 39 were enrolled in the BN group and 41 were enrolled in the LP group. As well, 39 calves received one dose of meloxicam and 41 were given 2 doses. For both the milk and NSAID treatments, 20 calves were BN with 2 doses, 19 calves were BN with 1 dose, 21 calves were LP with 2 doses, and 20 calves were LP with 1 dose. All calves enrolled in the study received the intended treatment depending on their group and were followed for the entire study period from birth to d 77 of age. All samples and measurements collected were used in the analysis. Milk consumption (L/d) over time by milk treatment group is illustrated in Figure 3; treatment groups were statistically different in milk consumption beginning on d 7 and were different until weaning at d 63 ($P < 0.01$). Moreover, calves on the BN group had greater ($P < 0.01$) average ME intake (Mcal/d) from birth until weaning (d 0–63) compared with the LP calves (BN ME/d: 5.89 ± 0.04 Mcal/d, 95% CI: 5.81–5.96, LP ME/d: 5.16 ± 0.04 Mcal/d, 95% CI: 5.09–5.24). There were no deviations from the trial protocol for treatment allocation, randomization, blinding, data collection, or analysis. All data collected and analyzed from this trial that are not reported in this manuscript, are reported in Supplemental File S1 (https://doi.org/10.5683/SP3/CHTHRJ).

Baseline Characteristics

Calf age on the day of disbudding ranged from 18 to 30 d. The mean age was higher in the LP group compared with BN and higher in the control group compared with extra NSAID (BN: 20.9 ± 0.13 d, LP: 21.6 ± 0.13 d; $P < 0.01$, control: 21.5 ± 0.11 d, extra NSAID: 21.1 ± 0.13 d; $P = 0.05$). No difference was detected in baseline values between the different treatment groups for MNT (BN: 6.65 ± 0.09 kgf, LP: 6.83 ± 0.08 kgf; $P = 0.18$, control: 6.77 ± 0.09 kgf, extra NSAID: 6.72 ± 0.09 kgf; $P = 0.68$) and haptoglobin concentrations (BN: 0.15 ± 0.001 mg/mL, LP: 0.15 ± 0.0009 mg/mL; $P = 0.25$, control: 0.15 ± 0.001 mg/mL, extra NSAID: 0.15 ± 0.0009 mg/mL; $P = 0.06$) or between the NSAID treatment groups in daily lying time (control: 1,096.3 ± 3.6 min/d, extra NSAID: 1,096.1 ± 3.5 min/d; $P = 0.97$), number of lying bouts (control: 19.2 ± 0.23 bouts/d, extra NSAID: 18.9 ± 0.24 bouts/d; $P = 0.29$), or average lying bout length (control: 59.0 ± 0.72 min/bout, extra NSAID: 60.6 ± 0.86 min/bout; $P = 0.16$) in the week before disbudding.

Primary Outcomes

Wound Diameter. The effect of milk treatment on wound diameter over time is illustrated in Figure 4 and the effect of NSAID treatment on wound diameter over time is illustrated in Figure 4. On the day of disbudding, the mean wound diameter was 18.8 ± 0.13 mm and was not different between the milk ($P = 0.70$) or NSAID ($P = 0.16$) treatment groups. On wk 3 after disbudding, BN calves had smaller wound diameters compared with LP calves ($P = 0.05$, $F_{20, 1546} = 217.5$) and from wk 4

to 8, BN calves had smaller wound diameters compared with LP calves ($P < 0.001$, $F_{20, 1546} = 217.5$; Figure 4). Beginning on wk 4 and until wk 8, calves that only received 1 dose of an NSAID had smaller wound diameters compared with calves that received 2 doses of an NSAID ($P < 0.01$, $F_{20, 1546} = 217.5$; Figure 4).

Wound Depth. The effect of milk treatment on wound depth over time is illustrated in Figure 4 and the effect of NSAID treatment on wound depth over time is illustrated in Figure 4. On the day of disbudding, the mean wound depth was 5.2 ± 0.10 mm and was not different between the milk ($P = 0.53$) or NSAID ($P = 0.93$) treatment groups. On wk 2 after disbudding, BN calves tended to have smaller wound depths compared with LP calves ($P = 0.09$, $F_{20, 1539} = 71.5$) and from wk 3 to 8, BN calves had smaller wound depths compared with LP calves ($P < 0.01$, $F_{20, 1539} = 71.5$; Figure 4). Beginning on wk 3 and until wk 8 calves that only received 1 dose of an NSAID had smaller wound depths compared with calves that received 2 doses of an NSAID ($P < 0.05$, $F_{20, 1539} = 71.5$; Figure 4).

Full Wound Contraction. The time to the healed and fully contracted stage (Figure 1) was evaluated, but very few wounds or calves reached this stage by the end of the 7 to 8 wk of follow-up. Of the 160 horn buds evaluated in this trial, 19 of them healed completely by d 59 (median time to healing of 53.7 d), 10 were from BN calves and 9 from LP calves, and 8 from calves that received 1 dose of NSAID and 11 from calves that received 2 doses of NSAID. Out of all of the calves enrolled in this trial (n = 80), only 3 calves had both of their wounds reach the healed stage by d 59 (median time to healing of 53.8 d; milk treatments: 1 in BN, 2 in LP; NSAID treatments: 1 in control group, 2 in extra NSAID group). Figure 5 depicts the time that wounds spend in each of the 8 stages of healing based on the scoring system in Figure 1 and the length of time since disbudding that these tissues were present for.

Re-Epithelization: Horn Bud Level Analysis. Of the 160 wounds assessed for this study, 87 of them (from 56 calves) reached the epithelium stage of healing by the end of follow-up (59 d). For the 87 wounds which re-epithelialized, the time for individual wounds to reach this stage ranged from 28 to 59 d after disbudding with a median time of 49.2 d. The Kaplan-Meier failure curve for time to re-epithelization by milk treatment at the horn bud level is illustrated in Figure 6, and the Kaplan-Meier failure curve for time to re-epithelization by NSAID treatment at the horn bud level is illustrated in Figure 7. At any time during the healing process, wounds of BN calves were more likely to reach the epithelium stage compared with wounds of LP calves (HR: 1.93; 95% CI: 1.18–3.14; $P = 0.008$), and wounds of calves on the control group that only received 1 dose of NSAID were more likely to reach the epithelium stage compared with wounds of calves on the extra NSAID group receiving 2 doses of NSAID (HR: 1.87; 95% CI: 1.15–3.05; $P = 0.01$). Wounds from BN calves had 3.9 times the odds of re-epithelizing by d 59 after disbudding compared with wounds from LP calves (95% CI: 1.33–11.2; $P = 0.01$), and wounds from calves on the control group receiving 1 NSAID dose had

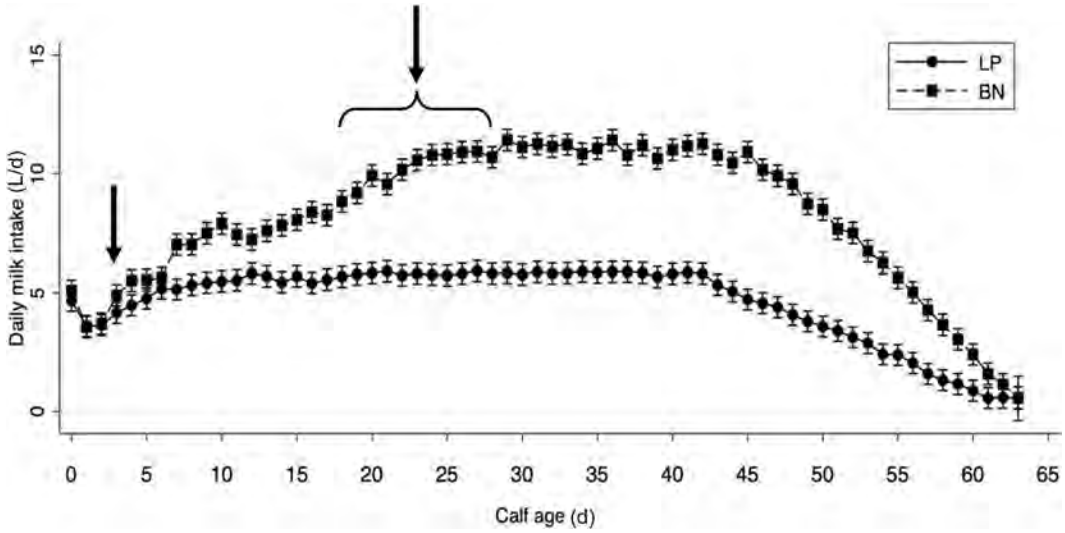

Figure 3. Total milk consumption (L/d; 95% CI) from birth to weaning of calves on the biologically normal plane of nutrition (BN) program (offered up to 15 L/d) and the limited plane of nutrition (LP) program (offered up to 6 L/d). The first arrow represents the time that the calves were trained on the Calf Rail system. The second arrow and bracket represent the time period when calves were disbudded (18–30 d of age).

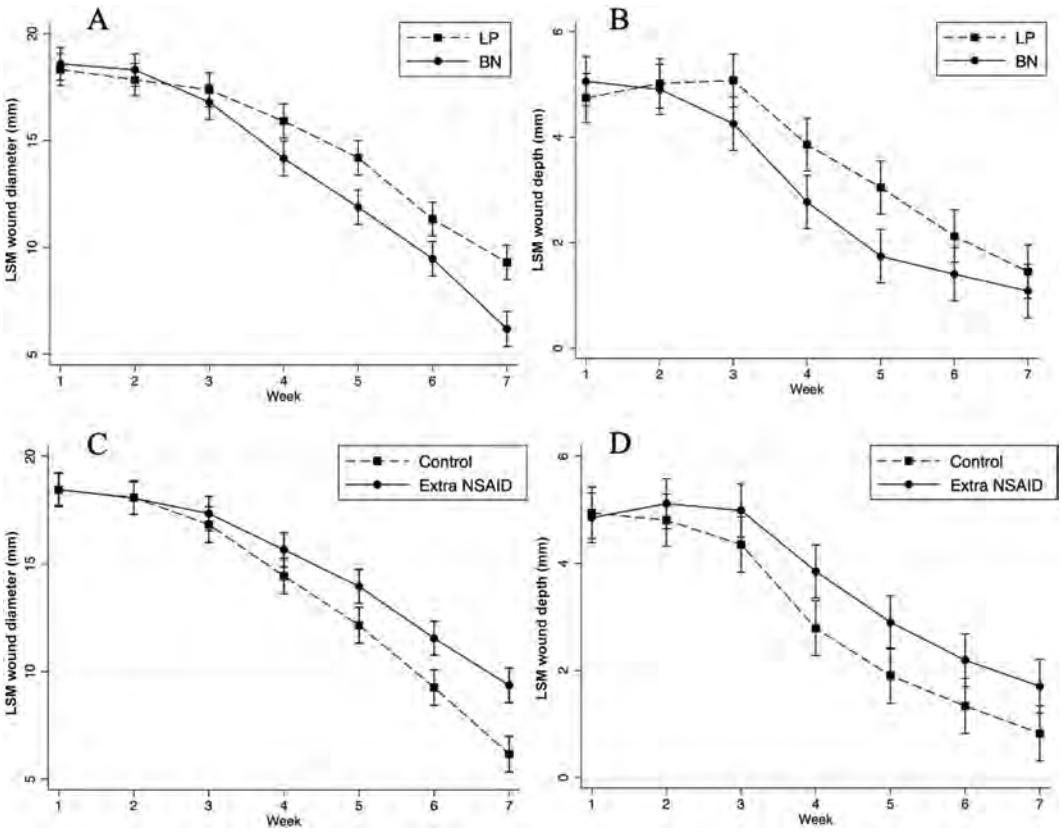

Figure 4. Least squares means (95% CI) of wound diameter (A) and depths (B; mm) of wounds from calves on the biologically normal plane of nutrition (BN) program (offered up to 15 L/d) and the limited plane of nutrition (LP) program (offered up to 6 L/d) over time relative to disbudding with a cautery iron. Least squares means (95% CI) wound diameter (C) and depths (D; mm) of wounds from calves on the control nonsteroidal anti-inflammatory drug (NSAID) group (1 dose 15 min before disbudding) and the extra NSAID group (1 dose 15 min before disbudding and 1 additional dose 3 d after disbudding) over time relative to disbudding with a cautery iron. Random effects for wound side nested within calf nested within calf room nested within disbudding date. Data from these figures included in Supplemental File S1 (https://doi.org/10.5683/SP3/CHTHRJ).

3.2 times the odds of having their wound re-epithelize by the end of follow-up compared with wounds from calves on the extra NSAID group (95% CI: 1.07 to 9.41, $P = 0.04$).

Re-Epithelization: Calf Level Analysis (Both Wounds). Of the 80 calves enrolled on this trial, 31 had both of their disbudding wounds reach the epithelium stage by the end of follow-up. For the calves who had both wounds reach this stage, the time for both wounds in one calf to re-epithelize ranged from 38 to 59 d after disbudding with a median time of 51.7 d. At any time during the healing process, BN calves were 134% more likely to have both wounds reach the epithelium stage compared with LP calves (HR: 2.34; 95% CI: 1.1–4.9, $P = 0.03$), and calves on the control NSAID group were 136% more likely to have both of their wounds reach the epithelium stage compared with calves on the extra NSAID group (HR: 2.36; 95% CI: 1.09–5.12; $P = 0.03$). Calves enrolled on the BN program had 3.6 times the odds of having both of their wounds re-epithelize by the end of follow-up (d 59) compared with LP calves (95% CI: 1.18–11.1; $P = 0.02$), and calves on the control NSAID group tended to have 2.8 times the odds of having both of their wounds re-epithelize by the end of follow-up compared with calves on the extra NSAID group (95% CI: 0.91–8.7; $P = 0.07$).

Presence of Purulent Discharge. The presence of purulent discharge at any point during the study was noted in 18 out of 160 wounds (15 calves) during the scoring of the wound healing photos, with 12 of these being calves with one wound having discharge and 3 with both. Due to small sample size of wounds with purulent discharge present, this variable was not modeled. Of these calves, 11 were from BN calves and 4 were from LP calves, and 11 were from calves on the control NSAID group and 4 were from calves on the extra NSAID group. All 18 of these wounds reached the epithelium stage of healing by the end of follow-up (d 59).

Secondary Outcomes

Haptoglobin Concentrations. There were no differences in haptoglobin concentrations detected between NSAID treatment groups at any time point ($P > 0.1$ for all categorical time interaction coefficients). There were no differences in haptoglobin concentrations detected between milk treatment groups from 60 min before disbudding (baseline) until 6 d after. However, there was a difference between milk treatment groups at d 7 after disbudding with BN calves having lesser haptoglobin concentrations compared with LP calves (BN adjusted mean: 0.083 mg/mL; LP adjusted mean: 0.113 ± 0.015 mg/mL; interaction coefficient: −0.03 mg/mL; 95% CI: −0.046 to −0.005; $P = 0.02$; $F_{16, 509} = 3.23$). However, this difference was driven by the presence of large outliers in the data and when the data were analyzed with these outliers removed, there was no longer a detectable association between milk treatment and haptoglobin concentrations. These outliers were investigated and were not reporting errors or from calves who were sick or had received an intranasal vaccine in the past week, or had purulent discharge, therefore the removal of these outliers could not be explained or justified.

Mechanical Nociceptive Threshold. There was no detectable treatment by time interaction for milk treatment and MNT values ($P > 0.1$ for all categorical time interaction coefficients). Regardless of time point, calves on the LP program had greater MNT values compared with BN calves (BN adjusted mean: 5.29 kgf; LP adjusted mean: 5.49 kgf; model coefficient: 0.19 kgf; 95% CI: 0.032–0.35; $P = 0.03$; $F_{19, 552} = 245.6$). Based on the interaction in the model, there were no detectable differences between the NSAID treatment groups 30 min before disbudding, directly before disbudding, or 4 h and 3 d after disbudding ($P > 0.1$, $F_{19, 552} = 245.6$). However, at 7 and 10 d after disbudding, calves that received an additional dose of NSAID tended to have greater MNT values compared with calves that only received 1 dose (control predicted adjusted mean 7 d: 1.39 kgf; extra NSAID predicted adjusted mean 7 d: 1.57 kgf; interaction coefficient at 7 d: 0.53 kgf,;95% CI: −0.015 to 1.08; $P = 0.06$; control predicted adjusted mean 10 d: 1.33 kgf; extra NSAID predicted adjusted mean 10 d: 1.47 kgf; interaction coefficient at 10 d: 0.5

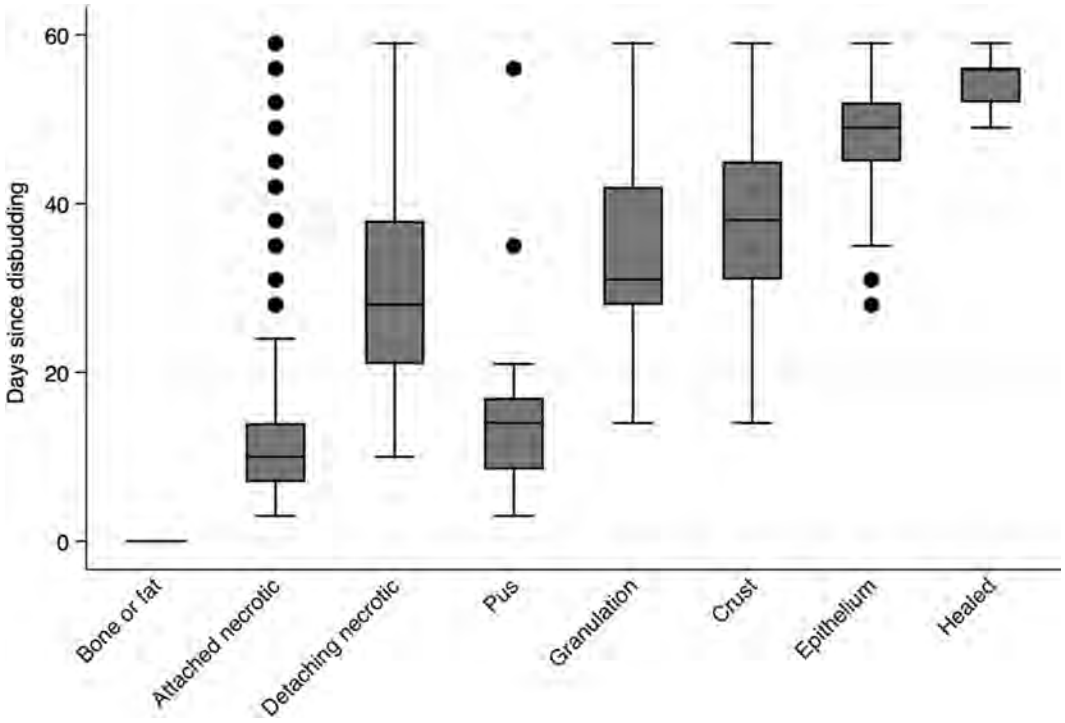

Figure 5. Days relative to cautery disbudding that each tissue type was observed. The box shows the interquartile range with the bottom of the box representing the 25th percentile and the top representing the 75th percentile. The line in the middle of each box represents the median, and the whiskers are the upper and lower limit (1.5× interquartile range). The black circles on the plot represent the outside values or outliers, which are any values outside of the range of the box and whiskers.

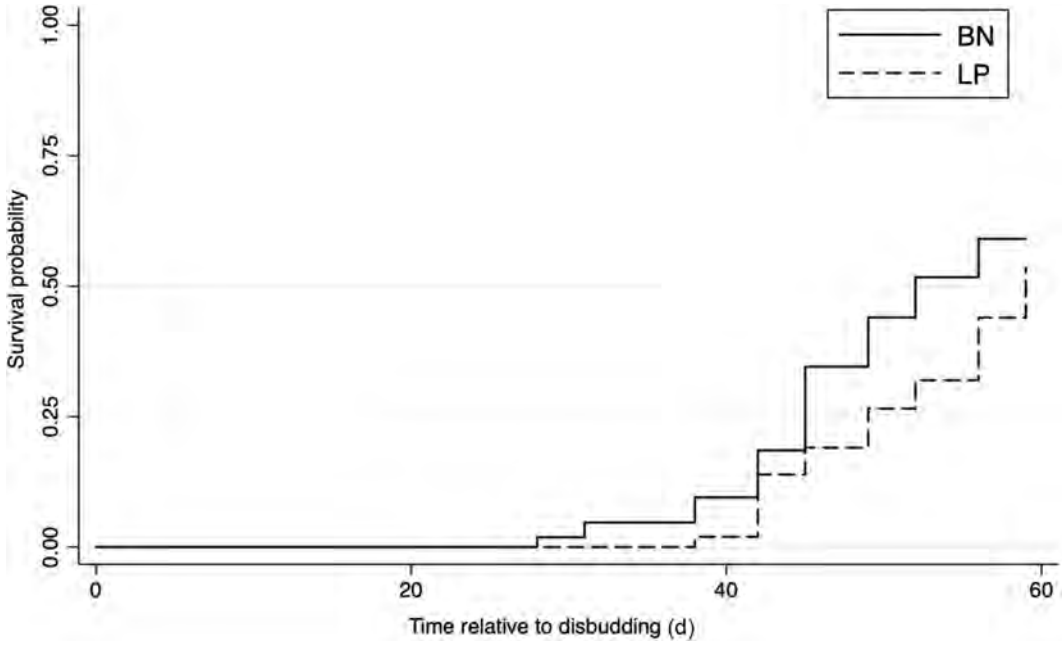

Figure 6. Kaplan-Meier failure curve of re-epithelialization at the horn bud level based on milk treatment group [biologically normal plane of nutrition (BN; offered up to 15 L/d) and the limited plane of nutrition (LP; offered up to 6 L/d)] over time relative to cautery disbudding (d). Values in this graph controlled for the effect of nonsteroidal anti-inflammatory drug treatment.

kgf; 95% CI: −0.055 to 1.05; $P = 0.08$; $F_{19, 552} = 245.6$), and at 17 d after disbudding, calves that received an additional NSAID had greater MNT values compared with calves that only received 1 dose (control adjusted mean: 1.37 kgf; extra NSAID adjusted mean: 1.61 kgf; interaction coefficient at 17 d: 0.59 kgf; 95% CI: 0.044–1.14; $P = 0.04$; $F_{19, 552} = 245.6$).

Lying Behavior. There was a milk treatment by time interaction for daily lying time (BN: 1,092.8 ± 1.15 min/d; LP: 1,094.4 ± 1.21 min/d), number of lying bouts (BN: 19.3 ± 0.08 bouts/d; LP: 18.6 ± 0.07 bouts/d), and average lying bout length (BN: 58.9 ± 0.26 min/bout; LP: 61.4 ± 0.25 min/bout) for the entire period that data were collected for (d 11 of age to d 77 of age; $P < 0.05$). Based on the interaction from the model, calves on the BN program had a decrease in their amount of daily lying time from d 11 to d 77 of age, whereas calves on the LP program had a slight increase in their amount of daily lying time from d 11 to 77 of age (interaction coefficient: −0.30 min/d; 95% CI: −0.45 to −0.16; $P < 0.001$; $F_{8, 209} = 7.6$). As well, calves on the BN program had fewer lying bouts in a d from d 11 to 77 of age and calves on the LP program had a slight increase in the number of lying bouts in a d from d 11 to 77 of age (interaction coefficient: −0.088 bouts/d; 95% CI: −0.097 to −0.080; $P < 0.001$; $F_{7, 161} = 95.0$). Last, from d 11 to 77 of age, calves on the BN program had longer average lying bout lengths and calves on the LP program had shorter average lying bout lengths (interaction coefficient: −11.0 min/bout; 95% CI: −14.0 to −7.95; $P < 0.001$; $F_{7, 156} = 64.5$).

The effect of NSAID treatment on daily lying time and average lying bout length in the wk after disbudding are described in Tables 1 and 2 respectively. Calves that received an extra NSAID spent less time lying in a day compared with control NSAID calves over the week after disbudding (Table 1; control predicted adjusted mean 6 d after disbudding: 810 min/d; 95% CI: 697–922, extra NSAID predicted adjusted mean 6 d after disbudding: 798 min/d; 95% CI: 687–910; control predicted adjusted mean 7 d after disbudding: 814 min/d; 95% CI: 702–927; extra NSAID predicted adjusted mean 7 d after disbudding: 800 min/d; 95% CI: 689–911; $F_{6, 164} = 6.5$). No significant interaction was detected between NSAID treatment and the number of lying bouts in a day over the week after disbudding ($P = 0.11$). Last, calves in the extra NSAID group also had shorter average lying bout lengths in the week after disbudding, whereas while calves in the control NSAID group had longer average lying bout lengths in this week ($P = 0.013$, $F_{8, 150} = 9.9$; Table 2). Interactions between milk and day and starter treatment and NSAID treatment were significant ($P < 0.05$, $F_{8, 150} = 9.9$) in the average lying bout length model as well (Table 2), therefore these were kept in the model to control for the effect of these treatments.

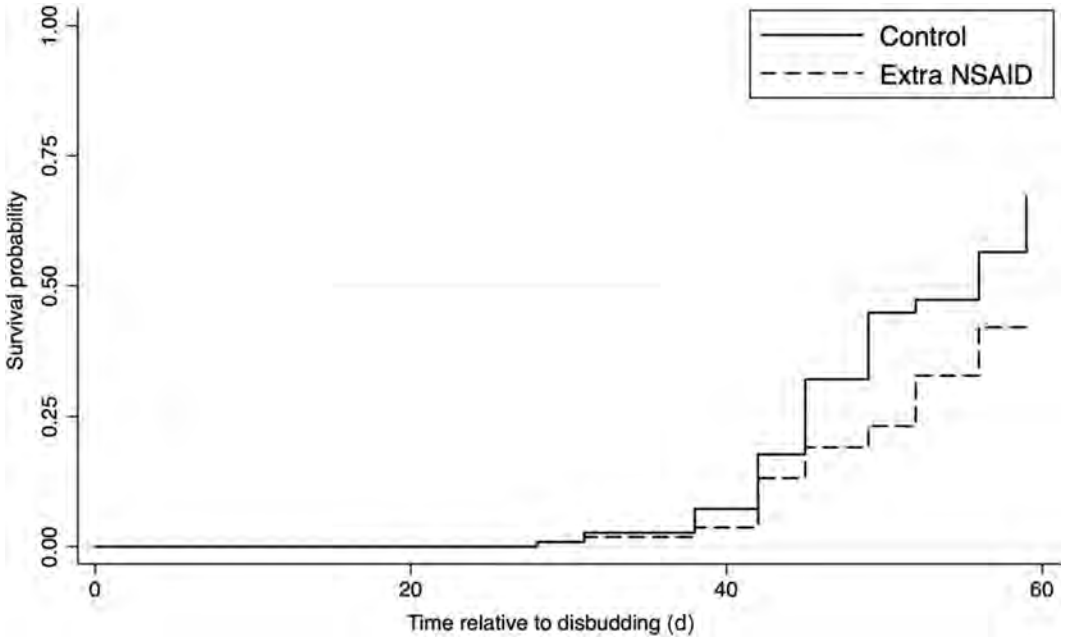

Figure 7. Kaplan-Meier failure curve of re-epithelialization at the horn bud level based on nonsteroidal anti-inflammatory drug (NSAID) treatment group [control (1 dose of NSAID 15 min before cautery disbudding) and additional NSAID (1 dose of NSAID 15 min before cautery disbudding and a second dose of NSAID 3 d after disbudding)] over time relative to cautery disbudding (d). Values in this graph controlled for the effect of milk treatment.

DISCUSSION

Wound Healing

Although not every calf in the current study had new epithelium form by the end of their follow-up (56/80 calves), of the ones that did, we noted that it took between 4 and 8 wk for this new epithelium to form. This was the first study to quantify full healing (fully contracted wounds) and only 12% of wounds reached this stage by the end of follow-up (7–8 wk after disbudding). However, based on past studies which have reported an average of 7 to 9 wk for wound re-epithelialization to occur (Adcock and Tucker, 2018; Adcock et al., 2019), we did not expect wounds to fully contract faster than this.

Effect of Milk Treatment

We found wounds of BN calves (15 L/d) healed faster (tissue type during healing, wound diameter, and wound depth) and formed new epithelium earlier compared with LP calves (6 L/d), due to the higher plane

Table 1. Output from final mixed-effect linear regression model for daily lying time (min/d) in the week after the disbudding procedure with random effects for calf nested within calf room nested within disbudding date

Item	Coefficient[1]	95% CI	*P*-value
Baseline	0.16	0.084 to 0.24	<0.001
Control[2]	Ref.	—	—
Extra NSAID[3]	6.96	−13.4 to 27.3	0.501
Limited plane[4]	Ref.	—	—
Biologically normal[5]	3.63	−12.8 to 20.1	0.660
Day since disbudding	4.59	2.46 to 6.71	<0.001
Age on day of disbudding (d)	4.63	0.52 to 8.76	0.028
NSAID × day	−3.01	−5.99 to −0.020	0.048

[1]Ref. = referent.

[2]Calves were given one dose of nonsteroidal antiinflammatory drug (NSAID) 15 min before cautery disbudding.

[3]Calves were given one dose of NSAID 15 min before cautery disbudding as well as an additional dose of NSAID 3 d after disbudding.

[4]Calves were offered up to 6 L of milk/d.

[5]Calves were offered up to 15 L of milk/d.

Table 2. Output from final mixed-effect linear regression model for average lying bout length/d in the week after the disbudding procedure with random effects for calf nested within calf room nested within disbudding date

Item	Coefficient[1]	95% CI	*P*-value
Baseline	0.05	−0.03 to 0.13	0.23
Control[2]	Ref.	—	—
Extra NSAID[3]	9.31	4.02 to 14.6	0.001
Limited plane[4]	Ref.	—	—
Biologically normal[5]	−7.03	−11.5 to −2.56	0.002
Whey-based starter	Ref.	—	—
Grain-based starter	5.04	0.78 to 9.30	0.021
Days since disbudding	1.26	0.60 to 1.93	<0.001
Milk × day	−0.91	−1.70 to −0.11	0.026
NSAID × day	−1.01	−1.79 to −0.22	0.013
Grain × NSAID	−9.96	−15.9 to −3.95	0.002

[1]Ref. = referent.

[2]Calves were given one dose of nonsteroidal anti-inflammatory drug (NSAID) 15 min before cautery disbudding.

[3]Calves were given one dose of NSAID 15 min before cautery disbudding as well as an additional dose of NSAID 3 d after disbudding.

[4]Calves were offered up to 6 L of milk/d.

[5]Calves were offered up to 15 L of milk/d.

of nutrition fed to the BN calves. This relationship between nutrition level and wound healing has also been noted in human literature (Williams and Barbul, 2003; Stechmiller, 2010; Wild et al., 2010). Researchers have reported that feeding higher than the conventional 10% BW milk allotment to calves and feeding milk more than once daily results in improved growth and reduced hunger (Jongman et al., 2020), as well as increased energy intake and weight gain (Jasper and Weary, 2002; Mirzaei et al., 2018). Although the calves in our study did not always consume the entire amount of milk that they were offered in a day, calves on the BN group drank significantly more milk daily beginning on d 7 of life until weaning and had greater ME intakes per day from birth until weaning compared with LP calves. During the healing process, purulent discharge was noted in a few of the wounds (15/160). The majority of these wounds (78%) were from calves on the BN program. This may have been a result of these calves being more active, which was noted in the lying behavior data and, therefore, may have been less careful of their wounds (Molony and Kent, 1997). However, this stems from descriptive data on a small sample size of purulent discharge observed during the data collection period.

Effect of NSAID Treatment

Although an increased level of milk intake in calves resulted in improved healing times, we also detected that providing calves with an extra NSAID 3 d after disbudding slowed the healing process (tissue type during healing, wound diameter, and wound depth). This finding has also been reported in mice (Huss et al., 2019) and humans (Kaushal et al., 2006; Anderson and Hamm, 2012) following wounds due to incisions. Tissue damage triggers the healing process which consists of coagulation, inflammation, and healing (Lisowska et al., 2018). There are many different intricate parts to all of these mechanisms that result in wound healing and the formation of new epithelium; however, NSAIDs have been shown to have a depressant effect on this process (Anderson and Hamm, 2012). Briefly, NSAIDs inhibit the production of inflammatory mediating prostaglandins, such as PGE_2, which reduces pain; however, NSAIDs also have an antiproliferative effect on skin and blood vessels which is what causes them to affect the healing process (Anderson and Hamm, 2012). Therefore, although NSAIDs are proven to reduce pain in humans (Kaushal et al., 2006; Anderson and Hamm, 2012), mice and rats (Huss et al., 2019), as well as calves (Winder et al., 2018; Gladden et al., 2019; Reedman et al., 2020), they appear to also have a suppressant effect on wound healing. This slower healing may also have been a result of the increased activity level noted in the 2-dose NSAID calves. Pain results in minimized behaviors that impede wound healing and maximizes protective behaviors (Molony and Kent, 1997). Therefore, by reducing pain, 2-dose NSAID calves may have been less protective of their wounds. Although both the LP and 2-dose NSAID treatments hindered the healing process, the lower plane of nutrition had a larger effect on this outcome compared with an additional NSAID dose. The effect size of milk treatment was larger compared with the effect size of the NSAID treatments when looking at the formation of new epithelium by the end of follow-up at both the wound and calf level. Therefore, although an additional dose of NSAID impeded the wound healing process, it did not affect it to the degree that a lower plane of nutrition did. As well, we also noted that wounds on calves receiving 2 doses of NSAID had much fewer instances of purulent discharge (22% of cases were from wounds on calves receiving 2 doses), which could be a result of decreased inflammation.

Haptoglobin

There is a lack of agreement across past disbudding research about the effect of pain control on haptoglobin concentrations in calves. Although some researchers have noted calves provided with analgesics alone or in combination with a local anesthetic have lower haptoglobin concentrations compared with calves with less or no pain control for both castration (Fisher et al., 1997; Earley and Crowe, 2002; Ballou et al., 2013) and disbudding procedures (Ballou et al., 2013; Erdogan et

al., 2019; Reedman et al., 2020), similar to the current study, other researchers have demonstrated no differences in haptoglobin concentrations when comparing pain control strategies for disbudding procedures (Allen et al., 2013; Mirra et al., 2018; Reedman et al., 2021). Although we did not detect a difference at any time between the NSAID treatment groups in the present study, we did detect that calves on the LP program had increased haptoglobin concentrations (indicator of inflammation) 7 d after disbudding compared with calves on the BN program. However, this detected difference was driven by the presence of large outliers in the data. Compared with haptoglobin concentrations in other studies (Reedman et al., 2020, 2021), the large values in our data were comparable to large values from these data sets as well, suggesting that haptoglobin concentrations could be quite variable from calf to calf (range in this study: 0.06–0.6 mg/mL). Perhaps haptoglobin concentration differences are more detectable with larger sample sizes and increased power due to this variation. These differences between studies suggest that haptoglobin concentrations may not be a reliable biomarker when evaluating and comparing pain control strategies for disbudding procedures in calves.

Mechanical Nociceptive Threshold

Effect of Milk Treatment. Based on our results, it appears that calves on the LP program were less sensitive to the MNT test compared with calves on the BN program, although there was no effect of milk treatment at any specific time during the 3 wk these measurements were collected for. The MNT is used to assess pain sensitivity in disbudding research, particularly with cautery disbudding (Heinrich et al., 2010; Stock et al., 2016; Adcock and Tucker, 2018). Past research has reported that during the healing process after disbudding, all tissue types are more sensitive compared with nondisbudded tissue and new epithelium (Adcock and Tucker, 2018; Alvarez et al., 2019). Although many researchers have reported differences in MNT values based on pain control method after disbudding (Heinrich et al., 2010; Espinoza et al., 2013; Stock et al., 2016), to our knowledge, very few if any researchers have reported differences in MNT values based on milk feeding level to young calves. There are several different reasons why calves on the LP program may have been less sensitive to the MNT test compared with calves on the BN program. This difference could be attributed to the improved healing time and shallower wounds in the BN calves compared with the LP calves during the time period when MNT measurements were being collected. Therefore, by decreasing healing time with a higher milk allotment to preweaning calves, their disbudding wounds might be in a stage of healing that is more sensitive compared with other stages. Although we are unsure whether this hypothesis has been investigated in human or animal literature, a study on wound healing in humans did report that opioid receptors affect mechanisms involved in wound healing and, thus, the pain from a wound helps to induce the healing process (Bigliardi et al., 2015).

Another potential reason for this difference in MNT between the milk treatment groups could be attributed to the calf's ability to respond to the test. Although the MNT test is effective at determining the sensitivity of the horn bud area and pain experience of a calf after disbudding (Heinrich et al., 2010; Espinoza et al., 2013; Stock et al., 2016), calves must also have the ability to respond to the test for it to be effective. Previous research in younger calves (1–9 d old) suggest that calves in their first week of life may have less ability to respond adequately to the MNT test (Karlen et al., 2019; Reedman et al., 2020). Although our calves were much older than this, the results reported by Karlen et al. (2019) and Reedman et al. (2020) do indicate that the effectiveness of the MNT test depends on the individual calf's ability to show a withdrawal response to the test. Therefore, it could be that the BN calves had more ability to respond earlier to the MNT test compared with calves on the LP program, due to their increased activity level. This raises the question whether the increased sensitivity noted in the BN calves is due to a potential improved ability to respond better to this pain, or if faster healing is associated with increased pain or sensitivity.

Effect of NSAID Treatment. The extra NSAID treatment in this study was administered to calves 3 d after disbudding, and no differences were detected between the NSAID treatment groups before this point in time. The half-life of meloxicam in calves is approximately 35 to 38 h, therefore this drug is typically effective and present in a calf's system for up to 3 d (72 h) after administration (Allen et al., 2013). It also takes approximately 14 to 15 h for meloxicam to reach its maximum plasma concentration in calves (Allen et al., 2013), which may explain why there was no difference in MNT values 3 d after disbudding; MNT values on this day were collected 4 h after the additional dose of NSAID was administered. However, similar to past research, we detected that calves provided with an additional NSAID had decreased MNT around their horn buds compared with calves provided with less pain control (Allen et al., 2013; Glynn et al., 2013). We detected these differences up to 17 d after disbudding (no differences were detected on d 14 after disbudding), whereas other researchers have only reported these differences 6 h after disbudding between calves that received no

meloxicam compared with those that did (Winder et al., 2018). Although this effect was significant ($P = 0.03$) 17 d after disbudding in our results, the difference in values between the treatment groups (0.59 kgf) was not a large effect biologically, as our MNT values ranged from 0.5 to 10 kgf. We evaluated MNT for only 3 wk after disbudding; however, it would be interesting for future research to assess potential differences in MNT for a longer period of time.

Adcock and Tucker (2018) reported that calves disbudded at a younger age (3 d compared with 35 d) can be more sensitive to MNT tests on their rump later in life due to a systemic increase in pain sensitivity. Similar results have been reported in other species such as rodents where younger animals are more susceptible to long-term changes in pain sensitivity (Walker et al., 2009). Although our calves were not this young (3 d of age) and we did not detect an effect of age at disbudding when evaluating MNT values between NSAID treatment groups, our results could suggest that by decreasing the pain experience of the calf through the provision of an extra NSAID for a couple of days after administration, calves were then less sensitive to the MNT test after the drug had worn off. Calves that were not provided with an additional NSAID could have remembered the test as being more painful without that additional pain relief and therefore reacted to the stimulation earlier compared with the calves that received the additional dose. However, it is unclear why this difference was not also observed at 14 d after disbudding. As well, we did not evaluate the concentration of this drug in the calf's system, so we do not know how long it was present after the second dose was given. Further research evaluating the effects of an additional NSAID on the pain of calves after disbudding would be beneficial for understanding these results.

Lying Behavior

Effect of Milk Treatment. Calves on the BN program were more active compared with calves on the LP program. This was evident with decreased daily lying times, fewer lying bouts in a day, and longer lying bout duration across time in BN calves compared with LP calves. Although these differences were small biologically, this interaction between milk treatment and time was present when examining lying behavior across the entire 8 to 9 wk that data were collected but was not present when evaluating the time around disbudding specifically. Our statistical models controlled for the effect of baseline lying behavior values in the week before disbudding when evaluating the effect of milk treatment in the week after disbudding. When this was controlled for, there were no differences between the milk treatment groups in the week after disbudding suggesting that the difference observed across the entire data collection period (d 11–77 of age) was due to an increase in activity in relation to greater milk intake rather than an effect of disbudding pain on lying behavior.

Effect of NSAID Treatment. Results from the present study indicate that in the week following disbudding, calves that received an extra NSAID were more active (decreased lying time, decreased average lying bout duration) compared with calves that only received one dose of NSAID. The effect of pain on long-term lying behavior has been evaluated in few studies. Sutherland et al. (2018b) followed calves for 48 h after cautery disbudding with and without a local anesthetic, and clove oil disbudding without a local anesthetic, and detected calves spent more time lying in a d 24 h after the procedure regardless of treatment group. Similarly, Heinrich et al. (2010) detected in the 5 h after cautery disbudding that calves given meloxicam in conjunction with a local anesthetic were less active compared with calves only provided with a local anesthetic. However, it has been suggested that when calves are in pain, they will display more protective behavior to minimize pain and assist in healing such as decreased activity (Molony and Kent, 1997). This was reported by Sutherland et al. (2018b) as well, where 24 to 48 h after disbudding control handled calves were more active compared with all disbudded calves who spent more time lying in a day compared with their baseline values. Our results, in conjunction with our MNT results, suggest that providing an additional NSAID to calves 3 d after the procedure could result in decreased pain for the animals in the 1 to 2 wk after the procedure.

CONCLUSIONS

The results indicate that restricted milk feeding (up to 6 L/d), as well as an additional dose of an NSAID 3 d after cautery disbudding, in preweaning heifer calves can slow the wound healing process; however, the latter has a lesser effect on this process comparatively. These results also demonstrate that the healing process after disbudding is quite long and variable between calves. Feeding a higher level of milk (up to 15 L/d) also resulted in more active calves with more sensitive wounds, and providing calves with an additional NSAID 3 d after cautery disbudding can decrease behavioral indicators of pain in calves in the 1 to 2 wk after the procedure. In addition to the many reported benefits of feeding calves a biologically normal plane of nutrition, this study demonstrates an additional effect of improved wound healing in calves. Further research

assessing the effects of an additional NSAID after disbudding would be beneficial for understanding the effect of this medication on pain and healing.

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ORCIDS

Cassandra N. Reedman https://orcid.org/0000-0003-3904-0993
Todd F. Duffield https://orcid.org/0000-0001-6035-4669
Trevor J. DeVries https://orcid.org/0000-0001-9364-2456
Kerry D. Lissemore https://orcid.org/0000-0003-2979-4708
Sarah J. J. Adcock https://orcid.org/0000-0003-0227-5369
Cassandra B. Tucker https://orcid.org/0000-0002-6014-444X
Sarah D. Parsons https://orcid.org/0000-0002-7325-5093
Charlotte B. Winder https://orcid.org/0000-0002-7314-3657

Brief Communication Communication brève

Evaluation of the effects of treating dairy cows with meloxicam at calving on retained fetal membranes risk

Nathalie C. Newby, David Renaud, Robert Tremblay, Todd F. Duffield

Abstract — Some non-steroidal anti-inflammatory drugs increase the risk of retained fetal membranes. This is the first study to investigate the effects of meloxicam on the risk of retained fetal membranes. Administration of meloxicam to dairy cattle immediately following calving revealed no differences in the incidence of retained fetal membranes between meloxicam-treated and untreated animals. There was no difference between the 2 groups in the incidence of periparturient diseases following calving. Meloxicam can be used on the day of calving in lactating cows without increasing the risk of retained fetal membranes.

Résumé — L'évaluation des effets d'une injection de méloxicam immédiatement après le vêlage chez la vache laitière sur le risque de rétention des membranes foetales. Certains médicaments inflammatoires non-stéroïdiens augmentent le risque de rétention de membranes fœtales. Cette étude est la première à examiner les effets du méloxicam quant au risque de rétention de membranes fœtales. Aucune différence n'a été notée dans le cas de rétention de membranes fœtales lors du vêlage chez la vache laitière entre les vaches qui ont reçu une injection de méloxicam immédiatement après le vêlage et celles qui n'ont rien reçu. De plus, il n'y avait aucune différence d'incidence de maladies périnatales observées suite au vêlage entre les deux groupes. On peut donc administrer du méloxicam aux vaches laitières le jour du vêlage sans augmenter le risque de rétention de membranes fœtales.

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Considering that mammalian neural elements and biological consequences of pain are essentially the same, it follows that cows feel parturition pain in a similar manner to humans; calving leads to inflammation which causes pain. There is limited work on the effects of analgesia in dairy cows at calving and only a few studies have measured the safety of administering the commonly used analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), at calving. A recent review suggested that further research on the use of NSAIDs in the post-calving cow is required, given that NSAIDs are likely to be under-used and sub-optimally prescribed during this period (1). Available NSAIDs that may be used for that purpose are aspirin, ketoprofen, flunixin meglumine, and meloxicam. Ketoprofen is predominantly a COX-1 inhibitor in dogs and humans (2,3), with a plasma half-life of 2 h after an intramuscular dose of 3 mg/kg body weight (BW) in cattle (1). Flunixin meglumine inhibits both cyclooxygenase isoforms COX-1 and COX-2, but is more selective for COX-1 in horses (4), and has a terminal half-life from 3.14 to 8.12 h after intravenous administration in cattle (5). Meloxicam has a preferential anti-COX-2 activity in horses, rats, humans, dogs, and cats (4,6), but its affinity has not been determined in cattle, in which it has a mean plasma half-life of approximately 26 h (7). COX-2 inhibition is thought to account for most of the therapeutic effects of NSAIDs, while the inhibition of COX-1 likely accounts for most of the undesirable side-effects of NSAIDs such as gastrointestinal irritation, renal toxicity, and inhibition of blood clotting (8). COX-2 has been shown to be involved in contractility during parturition and COX-2 inhibitors would have a negative impact on the contractility (9).

There have been a number of contradicting studies of the impact of NSAIDs in fresh dairy cows. The main findings from studies that evaluated the effects of flunixin meglumine immediately following calving were that there was a significant increase in the odds of having retained fetal membranes (10,11) and increased odds of being diagnosed with metritis after 14 d postpartum (10). Prostaglandin administration should be considered as a routine prophylactic for fetal membrane expulsion following caesarian surgery in animals with a placenta firmly attached to the uterus pre-surgery (11). Ketoprofen administered immediately after calving and 24 h later resulted in a tendency for fewer cases of retained fetal membranes and had no impact on other

Department of Population Medicine, University of Guelph, Guelph, Ontario N1G 2W1 (Newby, Renaud, Duffield); Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario L7L 5H4 (Tremblay).

Address all correspondence to Dr. Todd F. Duffield; e-mail: tduffiel@uoguelph.ca

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Table 1. Summary of parturient and postparturient events in 462 Holstein cattle that were either untreated (cow $n = 53$, 1st lactation heifer $n = 174$, total $n = 227$) or received 0.5 mg/kg BW meloxicam (cow $n = 46$, 1st lactation heifer $n = 189$, total $n = 235$) within the hour following calving up to 24 h recorded by the farm worker or veterinarian

Event	Meloxicam number of events for male calves	Meloxicam number of events for female calves	Meloxicam incidence of events total	Control number of events for male calves	Control number of events for female calves	Control incidence of events total	Chi-square *P*-value*
Calf gender	113	118	48.1%	102	113	44.9%	0.79
Missing gender information	4			12			
Calving difficulty:							
Missing calving score	6	2		1	2		
Missing calving score and gender information	4			11			
Unassisted	19	36	23.4%	15	25	17.6%	0.23
Easy	71	71	60.4%	71	78	65.6%	
Hard	16	8	10.2%	16	8	10.6%	
Surgery	1	1	0.85%	0	0	0	
Stillborn calves	8	15	11.5%	13	5	11.9%	0.86
Stillborn calves — missing gender information	4			9			
Twins	1	1	0.85%	1	0	0.44%	1.00
Retained fetal membranes	13	8	8.9%	14	8	10.6%	0.55
Retained fetal membranes — missing gender information	0			2			
Metritis	2	6	3.4%	5	3	4.4%	0.58
Metritis — missing gender information	0			2			
Mastitis	8	17	10.6%	14	15	13.2%	0.39
Mastitis — missing gender information	0			1			
Displaced abomasums	1	2	1.3%	3	2	2.2%	0.49

*Note: Fisher's exact test used where < 5 per any cell existed.

measures of uterine or reproductive health (12). However, this result may have been inadvertently confounded by more first parity animals being treated with ketoprofen (35% treated *versus* 26% non-treated) (12), with a possible lower risk of retained fetal membranes in first parity animals (13). Meloxicam administered within 12 h following calving in both heifers and cows resulted in no difference in milk yield, but in greater activity in heifers treated with meloxicam compared to heifers treated with the placebo; however, postparturient health events such as retained placenta were not reported (14).

While it is likely that there may be positive benefits of treating dairy cows post-calving with NSAIDs (especially cows that experience a dystocia), 2 important questions are the timing of administration post-calving and which NSAID is more appropriate. There have been reported health issues with administering flunixin meglumine on the day of calving (10,11), and no increased health risk to administering ketoprofen on the day of calving (12). This implies that there are no common effects for all NSAIDs on retained placenta following calving. The goal of this study was to evaluate the effects of meloxicam, a COX-2-selective NSAID, on the health of early lactation dairy cows when it was administered as soon as possible following calving. The hypothesis was that meloxicam treatment soon after calving would have no detrimental effect on the incidence of retained fetal membranes.

The present trial was conducted on a large commercial Ontario dairy farm that has a freestall barn with sand bedding, milking on average 900 animals (78% first lactation animals, 18% second lactation animals, and 4% 3rd lactation or greater) and calving over 3000 animals/y. The major part of the business is selling milking cows. Enrollment of Holstein cattle occurred from June to Oct 2011, and was approved by the Animal Care Committee, University of Guelph (AUP# 11R044). Animals were randomly assigned to receive either a single 0.5 mg/kg BW dose of meloxicam (Metacam 20 mg/mL solution for injection; Boehringer Ingelheim, Burlington, Ontario) subcutaneously (cow $n = 46$, 1st lactation heifer $n = 189$, total $n = 235$) or no treatment (cow $n = 53$, 1st lactation heifer $n = 174$, total $n = 227$) within 1 h following calving. Random number tables using repeating and balanced blocks of 30 animals were constructed using computer generated numbers. As cows calved they were assigned the next treatment indicated in the random number table. Treatment administration was conducted by maternity barn staff and recorded in the calving binder. The calf gender, the occurrence of twins, as well as calving difficulty (unassisted = cow calved on her own with no assistance; easy = 1 person pull with no mechanical assistance; hard = 2 or more people or with mechanical help; surgery = caesarean section) were recorded by hired maternity staff or the herd veterinarian immediately following calving. A calf was determined to be stillborn if it died within the first 24 h. The occurrence (or absence) of retained fetal membranes (defined in this study as placental separation that failed to occur within 24 h post-calving) or metritis within the first 14 d following calving [diagnosis included systemic signs of illness such as inappetence, depression, and fever > 39.5°C accompanied with fetid discharge from the vulva; (15)] was recorded for every cow by the herd manager. The herd manager was blinded to the treatment assignments at calving.

The management of this herd meant that cows/heifers were being sold to other farms for dairy production in early lactation and thus the majority (79%) of animals that calved were primiparous animals.

Sample size estimates were calculated to detect a 2-fold increase, based on studies that investigated flunixin meglumine (10,11), in retained fetal membrane risk, and a total of 225 animals per treatment group were required with a confidence of 95% and 80% power, based on a 9% expected frequency of retained placenta in the control group for sample size calculations. Statistical software was used (SAS version 9.3; SAS Institute Inc., Cary, North Carolina, USA). The chi-square analysis was used to screen disease outcomes and calving events for association with treatment. *A priori* it was determined that any association with a *P*-value ≤ 0.20 would be subjected to further analysis with logistic regression. The exception was retained placenta since this was the primary outcome and parity was forced into the model since it is a known confounder. Treatment effect for retained placenta was further evaluated using a logistic regression model controlling for potential confounding of other variables. The occurrence of twins, stillbirth, calving difficulty, parity, and calf gender were all included in a model and then removed in a stepwise backward elimination procedure. Each variable with the highest *P*-value was removed until the model contained only those variables that were significant ($P < 0.05$) or if removal caused more than a 25% change in the model coefficient for treatment effect on RP, with the exception of parity which was forced into the model.

Table 1 summarizes the parturient and postparturient events in both groups. Calf gender was split evenly between the 2 groups, and the majority of calvings were easy pulls and all levels of calving difficulty were similar between the 2 groups (Table 1). The incidences of twins and stillborn calves were similar in both groups (Table 1) and within the range of the stillbirth rates (between 0 and 17.3%) found in 2007 on 162 dairy farms in central and western Canada (16). The randomizations of treatment *versus* control between heifers and cows were successful as there were no differences between the proportion of animals in the treated *versus* control group within each parity group (80% treated *versus* 77% control in the heifer group and 20% treated versus 23% control in the cow group; $P = 0.32$). There were no differences in the incidence of periparturient disease between treatment groups (Table 1). The lack of difference between groups in the incidence of metritis in the first 14 d following calving suggests that there were no immediate negative effects of meloxicam on uterine health.

The results of the logistic regression model suggest that there are no detrimental effects of administering meloxicam in the hours following calving on the risk of retained fetal membranes [odds ratio (OR) = 0.83, 95% confidence interval (CI) = 0.44 to 1.54; $P = 0.55$]. Overall incidence of retained fetal membranes in this study was 8.9% in the meloxicam group and 10.6% in the untreated group. In the same statistical model there were no differences in the odds of having retained fetal membranes after controlling for parity (OR = 0.90; 95% CI = 0.48 to 1.69, $P = 0.73$), but there was an increased odds of retained fetal membranes if the calf gender was male (male OR = 1.95; 95% CI = 1.02 to 3.73, $P = 0.04$). There were no interactions with calf gender and treatment on retained fetal membrane risk. The current study had sufficient power to detect a 2-fold increased risk of retained fetal membranes. In fact, 2 of the flunixin meglumine studies reported a 3-fold increased risk of retained fetal membranes associated with treatment (10,11). The lack of significant difference between treatment groups for the incidence of retained fetal membranes in the present study is similar to the one seen in the study that provided ketoprofen following calving (12) and indicates that there are no negative impacts of meloxicam on the expulsion of fetal membranes. This difference in meloxicam effect on retained fetal membranes is puzzling because of its strong affinity to inhibit COX-2 rather than COX-1 (4) but further studies are required to confirm this phenomenon and determine the mechanism of meloxicam activity in cattle at parturition.

In conclusion, the administration of meloxicam to Holstein cows immediately after calving had no detrimental effect on either the risk of retained placenta or on post-partum metritis. The results of the present study indicate that meloxicam can be used immediately following calving with no increased risk of retained fetal membranes in primiparous cows. Future studies are required to investigate the analgesic and anti-inflammatory properties of meloxicam after calving for the cow's health and welfare, as well as potential cost benefits to the farmer.

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