National Organic Standards Board
Livestock Subcommittee Petitioned Material Proposal
Meloxicam
August 19, 2024

Summary of Petition:
In February 2024, the NOP received a petition to add meloxicam to the National List of synthetic substances allowed for use in organic livestock production 7 CFR 205.603.

Summary of Review:
Understanding the consistent need for high animal welfare standards, the Livestock Subcommittee (LS) promptly evaluated the petition for meloxicam. As it was presented in a format, not by manufacturers, but a wide swath of industry experts and stakeholders, the call for additional tools to alleviate animal pain in organic production was heard! Capitalizing on current expertise on the Livestock Subcommittee, LS allocated significant human capital to reviewing this petition while also upholding the standards of thorough, professional review.

Use:
Meloxicam is highly effective in treating acute pain from various veterinary procedures, including disbudding, debudding, dehorning, castration, or surgery, as well as managing chronic pain from conditions like lameness, arthritis, and other musculoskeletal issues. Meloxicam offers a prolonged therapeutic effect (half-life) within the animal's system, which often means a single dose is sufficient for acute cases, thereby enhancing the animal's welfare compared to other pain management drugs listed on the National List (NL). Available in oral tablet form with an extended half-life in tissues, meloxicam ensures longer intervals between treatments, making pain management easier and more efficient. This not only benefits the animal's well-being but also minimizes potential harm to the environment and the farm ecosystem.

Manufacture:
This petition is submitted by certified organic livestock producers and supporters who believe that adding meloxicam to the NL benefits organic producers, the livestock they care for, and the organic industry overall. No manufacturers were involved in or contributed to the creation of this petition. Consequently, the manufacturing information provided here is compiled from extensive online research, including sources such as the United States Food and Drug Administration (FDA), the United States National Institute of Health (NIH), the Chemistry Book, Merck Index, various scientific journals, and interviews. We cannot confirm that this information precisely describes 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). The FDA and NIH documents we were able to review regarding Meloxicam listed Benzothiazolo3(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.

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%.”

Excluded Methods
The manufacturing process of meloxicam is a chemical formulation and does not involve the potential use of excluded methods.

International Acceptance:

Canadian General Standards Board Allowed Substances List (CAN/CGSB 32.311-2020)
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.

European Economic Community (EEC) Council Regulation, EC No. 2018/848 and 2021/1165
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.”

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999)
While meloxicam is not specifically listed, the standard states that when veterinary drugs are used, the withholding period shall be twice the period of conventional standards.

International Federation of Organic Agriculture Movements (IFOAM)
While meloxicam is not specifically listed, the general principles state management practices should be directed to the well-being of animals, achieving maximum resistance against disease and preventing infections. Sick and injured animals must be given prompt and adequate treatment. Further, the standards note the well-being of the animals is the primary consideration in the choice of illness treatment. The use of conventional veterinary medicines is allowed when no other justifiable alternative is available. Withdrawal periods shall not be less than double of that required by legislation.

Japan Agricultural Standard (JAS) for Organic Production

While meloxicam is not specifically listed, the standard states that when veterinary drugs are used, the withholding period shall be twice the period of conventional standards.

Environmental Issues:

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

Ancillary Substances:

Meloxicam for oral use was patented in the US in 2005 but is now beyond its patent protection period. As the drug is produced and sold by various manufacturers in generic form, compiling a complete list of all possible ancillary substances, carriers, and excipients is impractical. Nevertheless, a typical list of excipients has been identified, and a link to this list is provided below. However, due to the numerous manufacturing sources, the list might not be exhaustive.

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).

Subcommittee Review:

The subcommittee as a whole evaluated this material over the course of multiple meetings. Conducting a thorough review across all areas of consideration, the subcommittee found no concerns with this material and propose that it be added to the national list of approved synthetic materials.

Category 1: Classification

1. Substance is for: **_____Handling __X_ Livestock**

2. For HANDLING and LIVESTOCK use:
    a. Is the substance **_____Agricultural** or **__X__ Non-Agricultural?**
    Describe reasoning for this decision using NOP 5033-2 as a guide:

    b. If the substance is **non-agricultural**, is the substance **____Non-synthetic** or **__X__ Synthetic?**

    c. Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources? [OFPA §6502(21)] If so, describe, using NOP 5033-1 as a guide:

Category 2: Adverse Impacts

1. What is the potential for the substance to have detrimental chemical interactions with other materials used in organic farming systems? [§6518(m)(1)]
Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) pain relief anti-inflammatory medication. NSAID medications can result in adverse side effects 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.

2. What is the toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment [§6518(m)(2)]?
Doses greater than 5 times the therapeutic dose can result in toxicity. Chronic use in some animals may cause toxicity. Signs and symptoms of toxicity include "vomiting, abdominal pain, melena (black, tarry stool), and diarrhea." 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.

3. Describe the probability of environmental contamination during manufacture, use, misuse or disposal of such substance? [§6518(m)(3)]
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.

4. Discuss the effect of the substance on human health. [§6517 (c)(1)(A)(i); §6517 (c)(2)(A)(i); §6518(m)(4)].
Meloxicam is an approved drug for human use. It is available by prescription and not available over the counter. Meloxicam should be taken according to the recommendation of a patient's physician.

5. Discuss any effects the substance may have on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock [§6518(m)(5)].
Meloxicam is metabolized to four biologically inactive metabolites and excreted in feces and urine. There are no known effects on soil organisms, crops, or livestock.

6. Are there any adverse impacts on biodiversity (§205.200)?
There are no reported adverse impacts on biodiversity. Meloxicam is an approved drug for humans and dogs. Meloxicam is a drug allowed for use in other livestock species in the US according to FDA regulations established under Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA).

<u>Category 3: Alternatives/Compatibility</u>
Below are the alternatives for pain management in livestock approved on the National List, or other natural remedies:

Flunixin (injectable and pour-on)
Flunixin injectable is approved only for intravenous use in cattle, and it can cause severe tissue reactions, leading to unpredictable drug withdrawal times or serious complications like abscesses and

clostridial infections. The pour-on version of Flunixin is easier to apply but requires careful handling to prevent absorption by the people administering it.

Aspirin (oral)
Aspirin, which is easy to give orally in pill form, is quickly metabolized in cattle, offering only up to six hours of pain relief per dose.

Other Remedies
Natural remedies, home remedies, and herbal tinctures often provide inconsistent and short-lived pain relief according to scientific studies. A 2022 study in the Journal of Dairy Science concluded that white willow bark is ineffective for pain relief in calves. Similarly, a 2021 study in Translational Animal Science found that herbal treatments given orally did not adequately manage acute pain in disbudded dairy calves and suggested that additional analgesics might be necessary.

Veterinarians are unlikely to use natural brand-name and home herbal tinctures, as they are not generally accepted as effective pain management methods under most dairy animal welfare programs.

Classification Motion:
Motion to classify meloxicam as synthetic
Motion by: Nate Powell-Palm
Seconded by: Kim Huseman
Yes: 5 No: 0 Abstain: 0 Recuse: 0 Absent: 0

National List Motion:
Motion to add meloxicam (CAS #-71125-38-7) at §205.603(a) As disinfectants, sanitizer, and medical treatments as applicable.

> In accordance with approved labeling for organic livestock; Also, for use under 7 CFR part 205, the NOP requires:
>
> (i) Use by or on the lawful written order of a licensed veterinarian; and
>
> (ii) A meat withdrawal period of at least two-times that required by the FDA

Motion by: Kim Huseman
Seconded by: Nate Powell-Palm
Yes: 5 No: 0 Abstain: 0 Recuse: 0 Absent: 0