Formal Recommendation
From: The National Organic Standards Board (NOSB)
To: The National Organic Program (NOP)

Date: October 24, 2024
Subject: Meloxicam - petitioned
NOSB Chair: Kyla Smith

The NOSB hereby recommends to the NOP the following:
Rulemaking Action: X

Statement of the Recommendation:
The NOSB classified meloxicam as a synthetic and passed a technical amendment to the original motion to strike "meat" from the annotation. The Board voted to add meloxicam to the National List at §205.603(a).

Rationale Supporting Recommendation
At the Fall 2024 NOSB meeting, the Board passed three motions relating to the meloxicam petition. The petition was presented to the Board in early 2024 by a group of producers, stakeholders, and veterinarians in the organic livestock community. Public comments and subsequent Board discussion during the meeting are pertinent to the document and are summarized here to provide context for the three motions that were passed.
The Livestock Subcommittee voted not to seek an outside TR as the petition was deemed sufficiently thorough to answer the questions posed in the TR template. The livestock subcommittee produced an appendix document that references where in the petition each of the TR questions is answered.

During the Fall 2024 NOSB meeting, the NOSB voted unanimously, or nearly unanimously, for each motion. Based on public comment and additional Board discussion, the NOSB agreed to make a minor technical correction to strike "meat" from the original annotation. The intent of the petition and view of the Board was to encompass all livestock - meat and/or milk producing animals. This oversight was caught after the document was published for review prior to the Board meeting.

The petition was presented by a knowledgeable coalition of organic producers, veterinarians and organic industry advocates who stand firm on best practices. Public comments in support of listing meloxicam cited the need for a safe and effective pain management tool in both meat and milk producing organic animals. Several veterinarians' written and oral comments stated that meloxicam extra-label drug use in livestock by veterinarians with a valid veterinarian-client relationship is allowed in the U.S. under AMDUCA (The Animal Medicinal Drug Use Clarification Act of 1994) regulations and can be easily administered by properly trained dairy farm personnel with a veterinarian's prescription. Stakeholders repeatedly mentioned the ease of administration of meloxicam compared to alternative pain

management options as well as effectiveness. A few dairy producers' comments also included concerns of aspirin, a currently approved pain management tool, after receiving a letter from the FDA this fall.

Withdrawal period was mentioned by several commenters. As written, "A withdrawal period of at least two-times that required by the FDA" is consistent with other pain management medications on the National List. There were public comments requesting more defined days of withdrawal as twice the FDA requirement may not provide specific enough detail for use and species. An oral commenter detailed how the listing for Meloxicam aligns with Animal Medicinal Drug Use Clarification Act and its implementing regulations published at Title 21, Code of Federal Regulations, Part 530 with specificity on days of withdrawal for livestock. There were advocacy groups and a handful of producers who requested the listing to be limited to 'under one year of age and for disbudding and dehorning purposes only' - thus limiting milking animals, injured adult animals, and practices such as castration to be excluded. The Board deliberated the need for all animals to receive pain management in accordance with veterinarian recommendations.

The petition had broad support by the Board. The NOSB weighed numerous public comments, oversight from other government agencies (FDA), and ultimately the need for best practices to lead animal welfare standards.

NOSB Vote:

Classification Motion:
Motion to classify meloxicam as synthetic
Motion by: Kim Huseman
Seconded by: Nate Powell-Palm
Yes: 14 No: 0 Abstain: 0 Recuse: 0 Absent: 1

Motion Passed

Technical Amendment:
Motion to accept the technical amendment on meloxicam to strike the word "meat" from the original motion
Motion by: Nate Powell-Palm
Seconded by: Kim Huseman
Yes: 13 No: 0 Abstain: 1 Recuse: 0 Absent: 1

Motion Passed

Listing Motion:
Motion to add meloxicam to the National List at §205.603(a)
Motion by: Kim Huseman
Seconded by: Nate Powell-Palm
Yes: 13 No: 0 Abstain: 1 Recuse: 0 Absent: 1

Motion Passed

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

TR Category	Found in petition, page number X or (P:x) Found in Appendix "Y", page numb X(Ay:x)
Identification of Petitioned Substance	P:1, 10, 15 A7: 265-266, 269 A12: 289-305
Summary of Petitioned Use	P: 5-7 A4: 129-131
Characterization of Petitioned Substance	
Composition of the Substance	P: 3, 8-9, 11-12 A7: 267
Source or Origin of the Substance	P: 8-9 A7: 267
Properties of the Substance	P: 5, 10-11, 16-18 A7: 237-270 A16: 347-360 A17: 364-365 A18: 366-379 A26: 415-418 A28: 423-424
Specific Uses of the Substance	P: 5-8, 10 A4: 130-131
Approved Legal Uses of the Substance	P: 5, 10, 12 A10: 278 A15: 337-346 A16: 347-360
Action of the Substance	P: 5, 6, 11-12, 16 A7: 251-252 A10: 278 A16: 347-360 A17: 365 A26: 415-418 A28: 423-424
Combinations of the Substance	P: 7, 9, 16,19 A4: 130-131 A11: 281 A26: 417-418 A30: 441-451 A31: 452-468 A32: 469-476
Status	
Historical Use	P: 5, 7-8, 10-12, 21 A4: 130-131 A7: 237-270

	A18: 366-378
OFPA/NOP	P: 9
International: CODEX	NA
International: EU	P: 13 A23: 408-409
International: Japan	P: 14-15 A25: 413-414
International: Etc…	Canada: P: 12, A21: 392-401 Australia: P: 12 New Zealand: P: 13, A22: 402-407 Switzerland: P: 13, A24: 410-412 Netherlands: P: 9, A11: 279-288
Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517[c][1][B][ii])? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?	(A)- P: 1,5-6, 10-12, 16 A7: 237-270 A16: 347-360 A17: 365 A18: 366-378 (B)-NA
Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant,	P: 8-9 A7: 267

animal, or mineral sources (7 U.S.C. § 6502[21]).	
Evaluation Question #3: Discuss whether the petitioned substance is formulated or manufactured by a chemical process or created by naturally occurring biological processes (7 U.S.C. § 6502(21)).	P: 8-9 A7: 267
Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518(m)(2)).	P: 16-18 A7: 246-252
Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518(m)(2)).	P: 9, 16, 17 A7: 246, 249 A28: 423-424
Evaluation Question #6: Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518(m)(3)).	P: 8 A5: 204-205, 209, 212 A7: 246-265
Evaluation Question #7: Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518(m)(1)).	P: 16 A26: 417-418 A28: 423-424 A29: 432-440
Evaluation Question #8: Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518(m)(5)).	P: 18 A16: 347-360 A26: 417-418 A29: 432-440
Evaluation Question #9: Discuss and summarize findings on whether the use of the petitioned substance may be harmful to the environment (7 U.S.C. § 6517(c)(1)(A)(i) and 7 U.S.C. § 6517(c)(2)(A)(i)).	P: 17-18 A7: 246-251 A16: 347-360 A29: 432-440

Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517(c)(1)(A)(i), 7 U.S.C. § 6517(c)(2)(A)(i)) and 7 U.S.C. § 6518(m)(4)).	P: 17-18 A7: 237-242 A28: 432-440
Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517(c)(1)(A)(ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518(m)(6)).	P: 5-6, 18 A1: 26-32 A2: 33-46 A3: 47-62 A4: 129-131 A30 :441-451 A31: 452-468 A32: 469-476 A33: 478-497
Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518(m)(6)).	P: 6,20 A3: 47-62

Note: Appendix 7 includes a great deal of the information requested in the TR template and should be a common reference for those so inclined.