



BEYOND PESTICIDES

701 E Street, SE ■ Washington DC 20003
202-543-5450 phone ■ 202-543-4791 fax
info@beyondpesticides.org ■ www.beyondpesticides.org

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Ms. Michelle Arsenault
National Organic Standards Board
USDA-AMS-NOP
1400 Independence Ave. SW.,
Room 2648-S, Mail Stop 0268
Washington, DC 20250-0268

Re. LS: Lidocaine and Procaine

These comments to the National Organic Standards Board (NOSB) on its Spring 2016 agenda are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

Current listings

§205.603(b) As topical treatment, external parasiticide or local anesthetic as applicable

(4) Lidocaine– as a local anesthetic. Use requires a withdrawal period of 90 days after administering to livestock intended for slaughter and 7 days after administering to dairy animals.

(7) Procaine– as a local anesthetic, use requires a withdrawal period of 90 days after administering to livestock intended for slaughter and 7 days after administering to dairy animals.

Proposal from Livestock Subcommittee

Motion to amend the Lidocaine listing as follows: (4) Lidocaine– as a local anesthetic. Use requires a withdrawal period of ~~90 days~~ 8 days after administering to livestock intended for slaughter and ~~7 days~~ 6 days after administering to dairy animals.

Motion to amend the Procaine listing as follows: (7) Procaine– as a local anesthetic. Use requires a withdrawal period of ~~90 days~~ 8 days after administering to livestock intended for slaughter and ~~7 days~~ 6 days after administering to dairy animals.

Comments during sunset 2017

Public comments supported the relisting of both lidocaine and procaine and the reexamination of the withholding period. Like other commenters, Beyond Pesticides supported the reexamination of the withholding period for both lidocaine and procaine.

New evidence

We have recently become aware of a new review of lidocaine that supports the current withholding period of 90 days. A recent assessment by the European Committee for Medicinal Products for Veterinary Use (CVMP) makes the following conclusions:¹

- It is confirmed that 2,6-xylylidine [metabolite of lidocaine] is a genotoxic carcinogen in rats and it is assumed that no threshold exists for genotoxicity. No NOEL has been established for carcinogenicity.
- 2,6-xylylidine can be further metabolised to DMHA and DMAP. These metabolites lead to the formation of reactive intermediates like a nitrenium ion or iminoquinone. These reactive intermediates have the potential to covalently bind to DNA.
- Lidocaine may undergo metabolism to 2,6-xylylidine in humans in intestines and liver. By consequence, even if 2,6-xylylidine would not be formed in the food producing species, the exposure to the parent substance lidocaine via food of animal origin may eventually cause consumer exposure to 2,6-xylylidine. Therefore there is a potential risk for genotoxic and carcinogenic effects to the consumer following the exposure to lidocaine.
- The calculation [of clearing from the animal] can be refined to take into account the first rapid absorption phase, as indicated in all plasma curves, and the slow terminal phase (with $t_{1/2}$ of 17.7 hours) that would become apparent after 20–24 hours. ... Most of the dose of lidocaine would have been eliminated during the first phase, i.e. on the first day after dosing, leaving approximately 0.1% of the 3000 mg dose entering the slow phase of absorption. The total elimination time for the 3 mg entering the slow phase is 44 days, leading to a total elimination time of 45 days. [Emphasis added.]
- Data from a new residue depletion study in cattle indicate that lidocaine and related residues are present in edible tissues and in milk at early time-points after treatment. However, modelling data indicate that by the minimum cascade withdrawal period of 28 days the total amount of residues remaining in the animal's body will be in the picogram range; even if an entire carcass could be ingested by a single consumer, exposure to residues would remain below the TTC [threshold of toxicological concern] of 0.15 µg.
- Regarding milk, the minimum cascade withdrawal period of 7 days does not result in the total elimination of residues or in the elimination of total body residues down to the TTC. To ensure that total residues in the cow's body are below this level requires an interval of 15 days between use of lidocaine and the taking of milk for human consumption. At this time point there is no risk to the consumer. For lidocaine and 2,6-

¹ B. Urbain and C.M. Madero, 2015. CVMP assessment report regarding the request for an opinion under Article 30(3) of Regulation (EC) No 726/2004: In relation to the potential risk for the consumer resulting from the use of lidocaine in food producing species. European Committee for Medicinal Products for Veterinary Use. April 10, 2015. Procedure no: EMEA/V/A/092.

xylidine, the total elimination time (i.e. the time taken for the last molecule to leave the cow) would be 52 days. This time is based on a worst case scenario in which the cow receives the maximum dose of 4 mg/kg and elimination proceeds at a uniform (slow) elimination rate characterised by a half-life of 17.7 hours.

- For pigs no residue data are available and it is therefore not possible to calculate residue levels that will remain following the cascade withdrawal period. However, since metabolism is comparable to that in cattle, it is expected that the minimum cascade withdrawal period of 28 days for meat is sufficient to ensure that residues deplete to negligible levels. Furthermore, considering that lidocaine is used for castration within the first weeks of life, therefore far from slaughter, the risk to the consumer is considered negligible.
- For horses, in the absence of residue data it is not possible to conclude with 100% certainty whether a withdrawal period of 0 days is safe. However in the absence of any new residue data, considering the very limited use currently authorised for lidocaine and the extensive metabolism, and considering that new in vitro data have further demonstrated that 2,6-xylidine formation in horses is less significant than in cattle, the risk to the consumer can be considered negligible.
- For horses, considering the very limited use currently authorised (for local/regional anaesthesia only), the extensive metabolism and the fact that new in vitro data suggests less significant production of 2,6-xylidine in horses than in other species, the risk of consumer exposure to residues of lidocaine in horse meat is considered very low. In view of this, the current MRL classification ('No MRL required' for horses and for local/regional anaesthesia only) for lidocaine remains appropriate and no risk mitigation measures are considered necessary. In addition it is also noted that the likelihood of animals being sent for slaughter immediately after treatment is very low, which will further reduce the risk of consumer exposure to residues.
- For cattle, considering that the estimated amount of lidocaine residues in the cow's body is negligible (about 10 pg) it can be considered that the minimum cascade withdrawal period of 28 days is appropriate. Therefore, no new risk mitigation measures are needed.
- Regarding milk, the safety associated with the minimum cascade withdrawal period of 7 days is uncertain as this time period is not sufficient to ensure that total residues remaining in the cow's body will be below the TTC of 0.15 µg. To ensure that total residues in the cow's body are below this level requires an interval of 15 days between use of lidocaine and the taking of milk for human consumption. At this timepoint there is no risk to the consumer.
- For pigs no residue data are available. However, considering that metabolism in pigs is comparable to that in cattle, it is expected that the minimum cascade withdrawal period of 28 days is sufficient to ensure elimination of residues to a safe level. Moreover considering that the use for castration takes place at a time far from slaughter, the risk to the consumer is considered negligible.

- It would seem appropriate to inform lidocaine users via specialised literature for veterinarians or via dedicated websites that an interval of 15 days between use of lidocaine and the taking of milk for human consumption is recommended.
- [Regarding xylazine, from which 2,6-xylidine is also formed:] The bioavailability and biotransformation of xylazine in humans following oral administration has not been characterised. However, as oral absorption in rats is nearly 100%, absorption by the oral route may be expected in humans. In addition 2,6-xylidine has been detected in urine following parenteral administration of xylazine in humans.
- Therefore there is a risk for genotoxic effects to the consumer following the exposure to xylazine. However considering the low exposure level (8 to 25 µg) one day after treatment of cattle and the extensive metabolism in cattle and horses, the risk is considered negligible. It is also noted that the likelihood of animals being sent for slaughter immediately after treatment is very low, which will further reduce the risk of consumer exposure to residues.

In consideration of these conclusions, and in particular those underlined above, the most precautionary waiting time would be 45 days, the time that is needed to remove all 2,6-xylidine from the body of the cow. Since the NOSB's policy has been to double the conventionally-established waiting time, the assessment supports the current waiting period of 90 days.

It is appropriate to use as a basis for the waiting period the time to complete elimination of 2,6-xylidine, since it is a genotoxic carcinogen with no threshold for action.

Conclusion

We recommend that the LS reconsider its recommendations in light of this new evidence. We support the animal welfare motivations to reduce the withdrawal period for a local anesthetic, but we believe that the assessment of the CVMP needs to be taken into account.

Thank you for your consideration of these comments.

Sincerely,



Terry Shistar, Ph.D.
Board of Directors