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European Medicines Agency
Dr. D. Mackay
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

Your letter	Your reference	The Hague, 21 December 2012
Casenumber	Our reference	
Handled by	Telephone (direct)	

Re:
Request for a scientific opinion

Dear Dr. Mackay,

Herewith, I would like to request a opinion from the Committee for Medicinal Products for Veterinary Use on a scientific matter concerning the evaluation of veterinary medicinal products, in accordance with article 30.3 of Regulation (EC) No 726/2004.

The matter relates to the substance lidocaine, which is included in Table 1 of the Annex of Commission Regulation (EU) No 37/2010 with a 'no MRL required'-status for horses, for local/regional anaesthesia only.

Although the substance has an MRL status for horses only, it is widely used in major species such as cattle and pigs under the cascade.

The MRL Summary Report states that other food producing species than horses were not included because the metabolism in other species was unknown. A particular concern was a metabolite of lidocaine, 2,6-xylidine, which was not observed in horses but it was not known whether this metabolite occurs in other food producing species. 2,6-Xylidine is considered to be a genotoxic carcinogen.

Recent research however, indicated that 2,6-xylidine is the main metabolite produced by primary hepatocytes and liver microsomes from pigs and cattle when exposed to lidocaine *in vitro* (Thuesen and Friis, 2012[1]). The presence of 2,6-xylidine in urine of pigs and cattle was confirmed after intravenous administration of lidocaine (personal communication C. Friis, 2012).

The carcinogenic risk for consumers of edible products from cattle and pigs treated with lidocaine under the cascade is unknown. A study is being initiated in the Netherlands to investigate the residues of lidocaine and 2,6-xylidine in tissues and milk of cattle following parenteral administration

[1] Thuesen, L.R., and Friis, C. (2012) In vitro metabolism of lidocaine in pig, cattle and rat. Poster presentation EAVPT Congress 2012, The Netherlands

representing the field use. Early sampling time points and time points relevant to the rules of the cascade (28 days for slaughter and 7 days for milk) will be included.

Although the results of the tissue and milk residue study in cattle are not available at present, the data available indicate a reason for concern. In order to decide if any actions are necessary on the EU level, e.g. related to the marketing authorisations and/or the MRL status, it is crucial to have a common understanding of the scientific conclusions on the hazards and consumer risks resulting from the use of lidocaine in food producing species. Therefore, the scientific opinion of the CVMP on the matter is requested.

The CVMP is requested to give an opinion on the risk for the consumer resulting from the use of lidocaine in food producing species. In reaching their opinion the CVMP may wish to consider the following points:

1. Can the CVMP confirm that 2,6-xylidine is a genotoxic carcinogen? From the information available, it appears that 2,6-xylidine is carcinogenic (carcinoma's at multiple sites), however, genotox studies suggest that not 2,6-xylidine but actually a further metabolite is responsible for the genotoxic action, as the results of *in vitro* studies were positive with metabolic activation only.
2. It appears that humans can metabolise lidocaine into 2,6-xylidine. Therefore, even if 2,6-xylidine is not formed in the food producing species (as in horses), the exposure to the parent substance lidocaine via food of animal origin may eventually cause consumer exposure to 2,6-xylidine. Does the CVMP consider that there is a consumer risk for genotoxic and/or carcinogenic effects following exposure to the parent substance lidocaine?
3. What is the consumer risk of exposure to lidocaine-related residues in food resulting from the use of lidocaine in horses, pigs, and cattle. Please note that withdrawal periods in horses would be 0 days and the use in other species 28 days for slaughter and 7 days for milk (according to the *current* rules of the cascade).
4. Does the CVMP consider it necessary to take risk management measures? If yes, what risk management measures and communication does the CVMP consider appropriate?
5. As 2,6-xylidine can also be formed from xylazine, does the CVMP see any consumer safety concern after human exposure to xylazine and/or it's metabolites?

Please note that lidocaine is used in human medicine (e.g. crèmes for local anesthesia, injection in dental care, eyedrops, pastilles for sore throat), and therefore the CVMP may wish to involve the CHMP.

As soon as the report of the residue study is available (mid 2013), I will make it available for the CVMP. However, the CVMP is asked to consider the need for risk management actions before these results have become available.

Yours sincerely,

F. Verheijen
Medicines Evaluation Board Agency
Head of Veterinary Medicinal Products Unit