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Committee for Medicinal Products for Veterinary Use

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Opinion of the Committee for Medicinal Products for Veterinary Use pursuant to Article 30(3) of Regulation (EC) No 726/2004

On the potential risk for the consumer resulting from the use of diethanolamine as an excipient in veterinary medicinal products for food-producing species

Basis for opinion

On 7 March 2018 Belgium presented to the European Medicines Agency ('the Agency') a request for an opinion from the Committee for Medicinal Products for Veterinary Use, on a scientific matter concerning the potential risk for the consumer resulting from the use of diethanolamine as an excipient in veterinary medicinal products for food-producing species, in accordance with Article 30(3) of Regulation (EC) No 726/2004.

Diethanolamine is used as a solvent in various veterinary medicinal products authorised nationally in the majority European Union Member States. In January 2018 the CVMP removed diethanolamine from the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (also known as the 'out of scope' list). The decision was based on concerns relating to carcinogenicity and genotoxicity as diethanolamine has been shown to have carcinogenic potential in mice and the available genotoxicity data did not allow a conclusion to be drawn on the relevance of the findings for humans. The International Agency for Research on Cancer (IARC) has classified diethanolamine as possibly carcinogenic to humans.

The removal of diethanolamine from this 'out of scope' list meant that there were veterinary medicinal products for food producing animals on the market that contained a substance for which the MRL status is not addressed.

While the CVMP had concluded that the continued inclusion of diethanolamine in the 'out of scope' list was not justified, it had not gone further in relation to quantifying the risks for the consumer, as such a comprehensive evaluation is not foreseen for consideration of (potential) 'out of scope' entries.

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Therefore Belgium requested the CVMP to give an opinion on the risk for the consumer resulting from the use of diethanolamine as an excipient in veterinary medicinal products for food-producing species and, in relation to this, to present its view on the need for an MRL evaluation for the substance.

In the scientific opinion, the Committee was requested to address the following points:

- Whether diethanolamine is a DNA reactive carcinogen. In 2013 diethanolamine was reviewed and classified as possibly carcinogenic to humans (group 2B) by IARC. However, at that time IARC was unable to conclude on the mechanism of carcinogenicity;
- If it was concluded that diethanolamine is a DNA reactive, whether this would mean that the risk to the consumer should be considered as unacceptable;
- If it was concluded that diethanolamine is not DNA reactive, whether it would be possible to establish a margin of exposure that would be acceptable from a consumer safety perspective. In relation to this question the CVMP was to note that the previous entry in the 'out of scope' list included the following restriction: *"at doses up to 0.3 mg/kg bw/day"*;
- On the basis of its scientific evaluation, the CVMP was asked to consider whether, in order to allow the use of diethanolamine in veterinary medicinal products for food-producing animals, a full MRL evaluation would be needed.

The procedure started on 14 March 2018.

Opinion

The Committee, having considered the matter, reviewed data from published literature, answers provided by stakeholders during the public consultation and data received from the marketing authorisation holders came to the following conclusions on the four questions raised in the request for an opinion.

Question 1:

Can CVMP confirm whether diethanolamine is a DNA reactive carcinogen? In 2013 diethanolamine was reviewed and classified as possibly carcinogenic to humans (group 2B) by IARC. However, at that time IARC was unable to conclude on the mechanism of carcinogenicity.

CVMP response:

The overall weight of evidence from negative genotoxicity tests performed in standardised systems, especially considering the *in vivo* mammalian micronucleus test[1] and the comet assay[2], clearly outweighs the research work performed with non-standardised systems. It can be concluded that diethanolamine is unlikely to be a DNA reactive carcinogen.

Irrespective of this conclusion, the possibility cannot be excluded that diethanolamine, under specific conditions such as low pH in the stomach or during food processing (heat), can be converted to the known genotoxic carcinogen N-nitrosodiethanolamine (NDELA). Nitrosamine formation *in vivo* is thought to occur as a result of a non-enzymatic reaction between a secondary amine and nitrosating agents nitrate/nitrite in the acidic environment of the stomach resulting in an unacceptable consumer risk from the ingestion of diethanolamine containing food.

[1] NTP TR 20 (1992). Technical Report on toxicity studies of diethanolamine. NIH Publication No. 92-3343. https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox020.pdf

[2] Beevers C, Henderson D, Lillford L. (2015) Investigation of sodium arsenite, thioacetamide, and diethanolamine in the alkaline comet assay: Part of the JaCVAM comet validation exercise. *Mutation Research,* **786–788**, 165–171.

Question 2:

If it is concluded that diethanolamine is a DNA reactive, does this mean that the risk to the consumer should be considered as unacceptable?

CVMP response:

It can be concluded that diethanolamine is unlikely to be a DNA reactive carcinogen. Therefore this question is no longer relevant.

Question 3:

If it is concluded that diethanolamine is not DNA reactive, is it possible to establish a margin of exposure that would be acceptable from a consumer safety perspective? In relation to this question it is noteworthy that the previous entry in the 'out of scope' list included the following restriction: "*at doses up to 0.3 mg/kg bw/day*".

CVMP response:

From the mouse carcinogenicity study[3] no no-observed-adverse-effect-levels (NOAEL) can be established. However it is possible to derive a lower bound of the benchmark dose confidence interval ($BMDL_{10}$) of 2.55 mg/kg bw per day for liver tumours and to derive a permissible daily exposure (PDE) of 0.425 µg/kg bw per day applying an overall uncertainty factor equal to 6000. Alternatively a PDE of 0.333 µg/kg bw per day may be calculated on the basis of the NOAEL for effects on choline (10 mg/kg) obtained from the study in mice involving 4-week dermal administration of diethanolamine and applying an uncertainty factor of 30000.

The lowest calculated PDE of 0.333 µg/kg compared to a worst-case estimate for consumer exposure indicates an unacceptable risk to the consumer even after a single administration of diethanolamine containing products. Consumer exposure estimates and the resulting risk increase if repeated treatments or injection site consumption are considered.

In conclusion, the margin of exposure that is established based on the PDE and the worst case exposure estimate is not acceptable. In the absence of residue data in target species demonstrating that carcinogenic residues are below the PDE, worst case scenario calculations indicate that consumer exposure to residues of diethanolamine would represent an unacceptable risk.

Question 4:

On the basis of its scientific evaluation, does the CVMP consider that, to allow the use of diethanolamine in veterinary medicinal products for food producing animals, a full MRL evaluation is needed?

CVMP response:

It would in principle be possible to undertake an MRL evaluation to consider the possibility of an entry for diethanolamine in Table 1 of Commission Regulation (EU) No 37/2010. However, the applicant would need to provide the necessary dossier, including residue depletion data in edible tissues and milk, showing that residues of concern (i.e. consumer exposure) do not occur at levels that would lead to exposure greater than the PDE. Residue data in food derived from treated animals would be needed showing that carcinogenic residue concentrations are much lower than estimated in worst case

[3] NTP TR 478 (1999) Technical Report on the toxicology and carcinogenesis studies of diethanolamine in F344/N rats and $B6C3F_1$ mice (dermal studies), NIH Publication No. 99-3968. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr478.pdf

exposure scenarios. In addition, the consumption of an injection site containing residues would need to be taken into account. The potential formation of nitrosamines would also need to be addressed.

If diethanolamine is to be further used in veterinary medicinal products, a MRL evaluation according to Regulation (EC) No. 470/2009, additionally addressing possible nitrosamine formation would be needed.

This opinion is forwarded to the European Commission, to Member States, to Iceland and Norway and to the marketing authorisation holders, together with its appendix.

The opinion will be published on the Agency website with its appendix.

Appendix 1: CVMP assessment report