



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/36933/2015
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report EPMAR Diethylene glycol monoethyl ether (All food producing species)

On 9 October 2015 the European Commission adopted a Regulation¹ establishing maximum residue limits (no MRL required classification) for diethylene glycol monoethyl ether in all food producing species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Diethylene glycol monoethyl ether is used as a solubilising agent and an absorption enhancer. The substance is known to be used in oral, topical and injectable formulations in several animal species as well as in human medicines and in cosmetics.

Diethylene glycol monoethyl ether had maximum residue limits already established (no MRL required classification) for all ruminants and porcine species².

Intervet International B.V. submitted to the European Medicines Agency an application for the extension of maximum residue limits for diethylene glycol monoethyl ether to poultry, on 22 August 2014.

Based on the original data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 12 February 2015, the extension of maximum residue limits for diethylene glycol monoethyl ether to poultry and the extrapolation to all food producing species.

Subsequently the Commission recommended on 16 July 2015 that maximum residue limits in all food producing species are established (no MRL required classification). This recommendation was confirmed on 6 August 2015 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 9 October 2015.

¹ Commission Implementing Regulation (EU) No 2015/1820, O.J. L 265, of 09 October 2015

² Commission Regulation (EU) No 37/2010 of 22.12.2009



Summary of the scientific discussion for the establishment of MRLs

Substance name:	Diethylene glycol monoethyl ether
Therapeutic class:	NO ENTRY
Procedure number:	EMA/V/MRL/003307/EXTN/0003
Applicant:	Intervet International B.V.
Target species:	Poultry
Intended therapeutic indication:	Not applicable (for use as an excipient)
Route(s) of administration:	Oral

1. Introduction

Diethylene glycol monoethyl ether belongs to the family of glycol ethers. It is an excipient used as a solubilising agent and an absorption enhancer. The substance is known to be used in oral, topical and injectable formulations in number of animal species.

The substance is also used in human medicines as well as in cosmetics.

Diethylene glycol monoethyl ether was previously assessed by the CVMP in 1998 and 2005. Although no ADI was established since no NOEL could be identified, the CVMP considered that overall the information available allowed the conclusion that there was no toxicological concern connected to the use of the substance in veterinary medicine and therefore concluded that there was no need to establish MRLs for diethylene glycol monoethyl ether (see published summary reports EMA/MRL/488/98-FINAL and EMA/CVMP/244224/2005).

Currently, diethylene glycol monoethyl ether is included in Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Diethylene glycol monoethyl ether	NOT APPLICABLE	All ruminants and porcine	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

Intervet International B.V. submitted an application for the extension of maximum residue limits to poultry to the European Medicines Agency on 22 August 2014. The substance is proposed for use in an oral formulation for administration to chickens via drinking water.

2. Scientific risk assessment

In the 1998 and 2005 CVMP assessments of diethylene glycol monoethyl ether the safety assessment was mainly based on public bibliographic data and residue depletion studies were not provided.

In the current extension application to poultry, the safety file has been updated with new bibliographic data. No residue depletion data have been submitted but a theoretical evaluation of the potential daily intake via consumption of meat and/or eggs from treated chickens has been provided.

2.1. Safety assessment

In the safety assessment of the substance carried out in 1998 no ADI was established since no NOEL could be identified. However, the CVMP considered that overall the information available allowed the conclusion that there was no toxicological concern connected to the use of the substance in veterinary medicine.

2.1.1. Overview of pharmacological properties

The pharmacological properties of diethylene glycol monoethyl ether were reviewed in previous CVMP evaluations. No additional data were reviewed for this extension application.

Pharmacodynamic properties including mode of action

Pharmacodynamic tests showed that diethylene glycol monoethyl ether had the following secondary pharmacodynamic effects: decreased heart rate (5 to 10%) and lowered blood pressure (5%) following intravenous administration in anaesthetised rats, cats and dogs at the lowest doses (46.4 mg/kg bw in rats and cats and 10 mg/kg bw in dogs), neuroleptic effects (climbing test and rod balance test in intraperitoneally treated mice, ED₅₀ was 3100 to 5000 mg/kg bw, the highest dose without effect was 1300 mg/kg bw), increase of hexobarbital sleeping time after oral administration in mice (for a 2-fold potentiation the ED₀₅ was 70 mg/kg bw and the ED₅₀ 700 mg/kg bw), and the EC₅₀ values for the spasmolytic effect measured on the isolated guinea-pig ileum were between 4600 and more than 10 000 mg/kg. With the exception of the statistically significant cardiovascular effects observed following intravenous administration, all the pharmacological effects were induced at extremely high doses or concentrations (of the order of at least 1 g per kg). The pharmacological effects observed after intravenous administration at doses similar to therapeutic doses were not considered relevant for the consumer safety evaluation.

Pharmacokinetic properties (laboratory animals)

According to available literature reviews, diethylene glycol monoethyl ether is absorbed by the airways, digestive tract and skin. The main metabolic pathway involves oxidation of the hydroxyl group to the corresponding acid, under the effect of hepatic alcohol/aldehyde dehydrogenases, and a less important pathway to complete biotransformation to carbon dioxide. Excretion occurs mainly by the kidneys. In man, 69% of the administered dose was reported to be eliminated in the urine within 12 hours, mainly in the form of (2-ethoxyethoxy) acetic acid. Diethylene glycol monoethyl ether is soluble both in water and in organic solvents, which suggests that it should have an oral bioavailability in man of about 100%. Considering the overall risk assessment of the molecule, the lack of kinetic information is considered negligible.

2.1.2. Calculation of pharmacological ADI, if relevant

No pharmacological effects of diethylene glycol monoethyl ether have been identified that are considered relevant for the consumer safety evaluation of the substance. Consequently, there is no need to establish a pharmacological ADI.

2.1.3. Overview of toxicology

Single-dose toxicity

The previous CVMP evaluations of diethylene glycol monoethyl ether indicate that the substance has low acute toxicity following oral administration. More recently published data on the substance support this conclusion. The lowest oral LD₅₀ values in the rat, mouse and guinea pig were 1920, 6580 and 3000 mg/kg bw, respectively.

Repeated dose toxicity

The studies previously assessed by CVMP include oral dosing 90-day toxicity studies in pigs, rats (two studies) and mice. Target organs of toxicity were the kidney and liver. No toxicity was reported at doses of 167 mg/kg bw/day in pigs, 250 and 500 mg/kg bw/day in the rat studies and 850 mg/kg bw/day in mice. Two 2-year studies in rats were also reviewed but both were poorly reported. None of these studies were considered to comply with the relevant standards and it was concluded that a NOEL for the purpose of establishing an ADI could not be identified. It was nevertheless concluded that the oral repeated dose toxicity of the substance was low.

The current application to extend the MRLs to poultry includes an additional 90-day oral toxicity study in dogs, performed to a high standard. Animals were administered diethylene glycol monoethyl ether by oral gavage at doses of 0, 400, 1000 and 2000 mg/kg bw/day. A NOAEL of 400 mg/kg bw/day was established based on significantly increased relative liver weight, increased alkaline phosphatase in blood and decreased sodium, chloride and creatinine in urine in the 1000 mg/kg bw/day group.

Reproductive toxicity, including developmental toxicity

A number of reproductive toxicity studies were reviewed as part of the previous CVMP evaluations. However, the studies and their reporting were not considered to comply with the relevant standards and consequently it was concluded that a NOAEL for reproductive toxicity could not be established. Nevertheless, the studies available at that time did not identify a health risk considered to be relevant to the use of diethylene glycol monoethyl ether as an excipient in veterinary medicines.

In addition to the previously reported studies, two additional studies have now become available. A fertility and general reproductive performance study in which 24 male and 24 female rats were administered diethylene glycol monoethyl ether by gavage at doses of 0, 300, 1000 and 2000 mg/kg bw/day for a pre-mating period (63 days in males and 14 days in females), during mating and up to day 7 of gestation. Based on reduced body weight gain seen at 2000 mg/kg bw/day the NOAEL for systemic toxicity was established as 1000 mg/kg bw/day. No specific reproductive toxicity was observed and the NOAEL for fertility and general reproductive performance is therefore 2000 mg/kg bw/day.

Developmental toxicity was investigated in the rat. Twenty five female rats were administered diethylene glycol monoethyl ether by oral gavage from day 6 to 17 of gestation at doses of 0, 300, 1000 and 2000 mg/kg bw/day. The dose of 2000 mg/kg bw/day was associated with reduced body weight gain and reduced food consumption in the dams. Minor skeletal findings (predominantly increased incidence of reduced ossification) representing transiently retarded development was seen in the 2000 mg/kg bw/day group and was the only developmental effect considered drug related. A NOAEL of 1000 mg/kg bw/day was identified for maternal and embryofetal toxicity. There was no indication of teratogenicity.

Considering all of the available results, it is concluded that diethylene glycol monoethyl ether has a low reproductive, maternal and foetal toxicity with NOAEL of 1000 mg/kg bw/day.

Genotoxicity and carcinogenicity

A number of genotoxicity studies were reviewed in the CVMP's previous evaluations. Weak mutagenic activity was reported at high concentrations in some tested *Salmonella typhimurium* strains (TA1535, TA1537, TA1538) with or without metabolic activation and in *Saccharomyces cerevisiae* (D7). In an *in vivo* unscheduled DNA synthesis (UDS) test rats were dosed with diethylene glycol monoethyl ether at doses of 800 and 2000 mg/kg bw by gavage. No induction of unscheduled DNA synthesis was seen in primary hepatocytes. Finally, no induction of micronuclei was observed in mouse bone marrow following 2 daily intraperitoneal injections of diethylene glycol monoethyl ether at doses of 1980 mg/kg bw.

An additional Ames test is now available, performed in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 with and without metabolic activation. Concentrations from 52 to 5000 µg/plate were tested and no evidence of genotoxicity was seen.

Finally, a structure activity analysis was undertaken and no alerts for carcinogenicity or genotoxicity were indicated for diethylene glycol monoethyl ether.

The previous CVMP evaluations concluded that, in view of the results of mutagenicity tests, carcinogenicity tests for the substance were not necessary. The additional data provided supports this conclusion.

Studies of other effects including immunotoxicity and neurotoxicity

No signs of immunotoxicity or neurotoxicity were observed in repeated dose toxicity studies. Therefore, no specific studies are considered necessary.

2.1.4. Calculation of the toxicological ADI or alternative limit

In the CVMP's previous assessments of diethylene glycol monoethyl ether no toxicological ADI was established as it was considered that an appropriate NOEL from which to derive the ADI had not been identified. However, based on the available information it was concluded that there was no toxicological concern connected to the use of the substance in veterinary medicine.

The safety dossier has now been updated and the additional information fully supports the previous conclusion that there is no toxicological concern relevant to use of the substance as an excipient in veterinary medicines. It remains the case that based on the available studies, many of which do not comply with the standards currently in force, an ADI for diethylene glycol monoethyl ether cannot be established.

2.1.5. Overview of microbiological properties of residues

No microbiological data were provided, which is acceptable as no microbiological effects are expected for a substance of this type.

2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected there is no need to establish a microbiological ADI.

2.1.7. Observations in humans

Studies in humans relate to the use of diethylene glycol monoethyl ether in cosmetics products and therefore focus on dermal exposure. These studies are not considered relevant for the consumer safety evaluation of the substance in relation to its use in veterinary medicinal products.

2.1.8. Findings of other EU or international scientific bodies

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated diethylene glycol monoethyl ether in 1976, 1982 and 1995, in relation to its use as a carrier solvent for flavours. JECFA estimated that consumer intake of the substance as a result of this use is 15 mg/person (0.25 mg/kg bw/day). Based on the available data JECFA was not able to establish an ADI for the substance.

The Scientific Committee on Consumer Safety (SCCS) evaluated diethylene glycol monoethyl ether in relation to its use in cosmetics in 2013 and considered that total daily systemic exposure to the substance resulting from its use in cosmetics is 3.52 mg/kg bw/day. The relevant studies reported in the SCCS evaluation are reported elsewhere in this report and in the previous CVMP evaluations for the substance.

The US Environmental Protection Agency (EPA) reviewed the toxicity of diethylene glycol monoethyl ether in 2009 and 2011. The 2011 report indicates that the substance is chemically similar to ethylene glycol and diethylene glycol, which have similar toxicity potential to diethylene glycol monoethyl ether and act on the same target organs of toxicity (kidney and liver). It noted that no tumours had been seen in any of the long term studies in mice and rats and that it was not mutagenic *in vivo*. The 2011 assessment established a chronic dietary oral reference dose of 2.0 mg/kg bw/day based on a NOAEL of 200 mg/kg bw/day reported to have been established in a reproduction toxicity study in rats and applying a safety factor of 100.

2.1.9. Overall conclusions on the ADI

The establishment of pharmacological and microbiological ADIs is not considered necessary for diethylene glycol monoethyl ether. The previous CVMP evaluations for the substance considered that, due to the limitations of the available dataset, it was not possible to establish a toxicological ADI but that the available data had demonstrated that there was no toxicological concern relevant to use of the substance as an excipient in veterinary medicines. The additional data reviewed as part of this extension application supports this conclusion.

2.2. Residues assessment

No pharmacokinetic or residue depletion studies in the target animal species have been performed with diethylene glycol monoethyl ether.

2.2.1. Pharmacokinetics in target species

No pharmacokinetic studies in the target animal species have been performed with diethylene glycol monoethyl ether.

2.2.2. Residue depletion studies

No residue depletion studies in the target animal species have been performed with diethylene glycol monoethyl ether. No marker residue has been identified and no ratio of marker to total residues has been estimated.

2.2.3. Monitoring or exposure data

No monitoring or exposure data relevant to the use of diethylene glycol monoethyl ether in poultry were available.

2.2.4. Analytical method for monitoring of residues

On the basis that a “No MRL required” classification for diethylene glycol monoethyl ether in poultry was intended, no analytical method for monitoring of residues has been provided.

2.2.5. Findings of other EU or international scientific bodies

No relevant report relating to residues of diethylene glycol monoethyl ether in poultry was identified.

3. Risk management considerations

3.1. Potential effect on the microorganisms used for industrial food processing

As the substance is not expected to possess antimicrobial activity no effects on microorganisms used for industrial food processing are expected.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

Diethylene glycol monoethyl ether is currently included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 with a “No MRL required” classification in all ruminants and porcine species on the basis that:

- no pharmacological activity considered biologically relevant in respect of consumer safety was identified for the substance,
- it is of low oral toxicity,
- the available information indicates that it is rapidly absorbed and excreted after intravenous and intramuscular injection.

The first two bullet points above are also considered to be relevant in relation to its proposed use in poultry. While the route of administration in poultry is not expected to be intravenous or intramuscular injection, the substance is still expected to be rapidly absorbed and excreted. Overall, the available data support the conclusion that the establishment of numerical MRLs for diethylene glycol monoethyl ether in poultry species is not necessary for the protection of human health.

Calculation of theoretical daily intake of residues

Diethylene glycol monoethyl ether is proposed for use as an excipient for use in veterinary medicinal products for administration to poultry, and it could be used at different concentrations and administered to poultry at different doses. It follows that a definitive exposure calculation covering all exposure scenarios that may occur as a result of its use in products for administration to poultry cannot be provided.

Based on a hypothetical formulation for an oral administration to poultry containing 30% diethylene glycol monoethyl ether (similar to the concentrations used in cattle products), and assuming (i) 100% absorption following oral administration, (ii) no metabolism and excretion of the substance following its administration, and (iii) equal distribution around the body, it can be estimated that the maximum consumer exposure to residues in poultry tissues and eggs would be 0.156 mg/kg bw/day (9.36 mg/person per day). The above worst case calculation is also considered to be applicable following repeated administration of products to poultry as diethylene glycol monoethyl ether is rapidly eliminated and so will not accumulate in tissues or eggs. The worst case consumer exposure calculation results in an exposure level that is 22.5 fold lower than the total daily systemic exposure of 3.52 mg/kg bw estimated as a result of the use of the substance in cosmetic products, 12.8 fold lower than the chronic oral reference dose of 2 mg/kg bw/day established by the US EPA, 801 fold lower than the lowest dose (125 mg/kg bw/day) at which no clinical signs were observed in humans, 1070 fold lower than the lowest dose (167 mg/kg bw/day) with no adverse effects in a 90-day oral administration study in pigs, and 2564 fold lower than the dose (400 mg/kg bw/day) with no adverse effects in a 90-day oral toxicity study in dogs.

These worst case calculations further support the conclusion that the "No MRL required" classification for diethylene glycol monoethyl ether can be extended to poultry.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009, the CVMP considered the possibility of extrapolating its recommendation on maximum residue limits for diethylene glycol monoethyl ether in all ruminants, porcine and poultry to other food producing species and commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as described below.

Animal species/ food commodities	Extrapolation possible (Yes/No)	Justification
All food producing species	Yes	The metabolism of diethylene glycol monoethyl ether is not expected to differ substantially across species. A 'No MRL required' classification has been granted with regard to all ruminants and porcine species and is now recommended for poultry. The use of the substance in other food producing species is not expected to have a significant impact on consumer exposure and extrapolation to all food producing species is therefore justified.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- diethylene glycol monoethyl ether was previously considered to be of low oral toxicity and this conclusion is supported by the additional data now available,
- the available information indicates that diethylene glycol monoethyl ether is rapidly absorbed and excreted,
- diethylene glycol monoethyl ether is already included Table 1 (allowed substances) of Regulation (EU) No 37/2010 for all ruminants and porcine species;

the Committee recommends the extension of maximum residue limits for diethylene glycol monoethyl ether to poultry and their extrapolation to all food producing species in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Diethylene glycol monoethyl ether	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

4. Background information on the procedure

Submission of the dossier

22 August 2014

Steps taken for assessment of the substance

Application validated:

17 September 2014

Clock started:

18 September 2014

CVMP opinion adopted:

12 February 2015