EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 June 2021
EMA/275956/2021
Committee for Medicinal products for Human Use (CHMP)

Opinion of the SWP regarding Diethanolamine and coconut oil diethanolamine condensate as excipients

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information

Diethanolamine and coconut oil diethanolamine condensate are used as excipients in various topically applied human medicinal products.

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: 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 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 was not addressed. An art 30(3) referral was triggered to request the opinion of the CVMP on the potential risk for the consumer resulting from the use of diethanolamine as an excipient in veterinary medicinal products for food-producing species. The CVMP concluded that 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.

In light if these discussions in the veterinary context, on 16 May 2018 the CMDh asked the CHMP to forward the following question to the attention of SWP for further assessment focusing on the relevance for human medicines.

2. Questions to the SWP

Diethanolamine and Coconut oil diethanolamine condensate are used as excipients for several topically applied medicinal products, for long term treatment.

Taking into account

- The revised IARC classification of diethanolamine and coconut oil diethanolamine condensate as possibly carcinogenic to humans (group 2B) by IARC (http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-004.pdf and http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-005.pdf).
- The CHMP scientific article 5(3) opinion on "The Potential Risks of Carcinogens, Mutagens and Substances Toxic to Reproduction (CMR)" (Doc.Ref.EMEA/CHMP/SWP/146166/2007), that recommends that appropriate safety measures would be taken on the concerned medicinal product(s) consistent with the current legal and regulatory framework in order to protect public health.
- The conversion (nitrosation) of secondary amines, such as diethanolamine, into N-nitrosamines that may be carcinogenic, concern by which, dialkanolamines and their salts are prohibited for use in cosmetic products by the EC: Cosmetics directive 76/768/EEC recast in Regulation (EC) No 1223/2009, Annex II (total ban), entry 411 "Secondary alkyl- and alkanolamines and their salts".

SWP was requested to evaluate the relevance of the available genotoxicity and carcinogenicity data for humans and its acceptability of using in medicinal products

On 6 October 2020, the CMDh asked the CHMP to forward the following additional question to the SWP:

Which retention factor(s) would be acceptable in the risk assessment for DEA in rinse-off products, taking into account the health condition of the skin?

3. Opinion

3.1. Overall summary and SWP response

3.1.1. Relevance of the genotoxicity and carcinogencity studies

Regarding genotoxicity, based on the available information in the recommended standard genotoxicity test battery in vitro and in vivo, it can be concluded that diethanolamine is not likely to be a DNA reactive carcinogen. Coconut oil diethanolamine condensate was also negative in the standard test battery of in vitro genotoxicity studies. The induction of micronuclei in the in vivo micronucleus assay following exposure to coconut oil diethanolamine condensate cannot be attributed to the presence of diethanolamine, taking into account that an in vivo micronucleus assay conducted with diethanolamine was negative. In this context it needs to be considered that the polar nitrosamine, N-nitrosodiethanolamine, was detected at a concentration of 219 ppb in this study, which was considered consistent with the anticipated composition of commercial coconut oil acid diethanolamine condensate. No N-nitrosodiethanolamine was detected in the diethanolamine solution above the 1 ppb limit of detection.

In 2013, the International Agency for Research on Cancer (IARC) classified diethanolamine (DEA) and coconut oil diethanolamine condensate as possibly carcinogenic to humans (group 2B) and concluded that there is sufficient evidence in experimental animals for the carcinogenicity of diethanolamine and coconut oil diethanolamine condensate.

This classifications were based on carcinogenicity findings from 2-year dermal studies in mice conducted by the US National Toxicology Program (NTP) where either diethanolamine or coconut oil diethanolamine condensate were applied topically at doses of 40, 80 or 160 mg/kg bw diethanolamine or 0, 100 and 200 mg/kg coconut oil diethanolamine condensate diluted in 95% ethanol, for 5 days per week over 103 weeks. All doses of diethanolamine were considered to have caused significant increases in hepatocellular neoplasms in male and female mice, with a positive trend seen in the incidences of renal tubular adenoma at all doses in treated males. IARC noted that "tumours of the kidney and hepatoblastomas are rare spontaneous neoplasms in experimental animals". The pattern of tumour response observed for coconut oil diethanolamine condensate is the same as that of diethanolamine applied topically to mice. The content of unreacted diethanolamine in the coconut oil diethanolamine condensate was estimated to be approximately 18.2%, resulting in 36.4 mg DEA administered at the highest dose. The increased incidence of neoplasms in mice was associated with the level of free diethanolamine that was present in the solutions of diethanolamine condensate tested.

Based upon further analysis, it is considered that the dose dependent occurrence of hepatocellular carcinomas (and hepatoma) in the mouse carcinogenicity studies cannot unequivocally be attributed to diethanolamine and confounders including the use of ethanol as a vehicle, mouse strain specificity and differences in toxicokinetics (percutaneous absorption) between species cannot be disregarded. However, incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) in all groups receiving diethanolamine and of hepatocellular carcinoma and hepatoblastoma in males were significantly increased compared to vehicle (i.e. ethanol) treated controls. Additionally,

size and multiplicity of neoplasms in diethanolamine treated animals were greater than in the vehicle controls.

Taking into account that ethanol is not associated with kidney tumours in experimental animals (including mice) and humans (IARC) the effects observed might not be entirely attributed to the presence of ethanol.

Regarding the mechanism of carcinogenicity, induction of choline deficiency has been proposed as the means by which diethanolamine induces liver neoplasms in mice. This hypothesis would support an epigenetic mode of action. Literature data might suggest that this mechanism could also be relevant for the mouse kidney tubule adenoma/carcinomas. In a study in which male Sprague Dawley rats were fed a choline deficient diet for 6 days, followed by a normal diet for up to 119 days, acute renal lesions consisting of tubular epithelial cell necrosis were observed immediately after being fed a choline-deficient diet (Keith and Tryphonas 1978). Chronic renal lesions consisting of interstitial nephritis characterised by fibrosis and scarring were observed 28-119 days after being fed the choline-deficient diet. The proximal convoluted tubule was most severely affected. Hepatic lesions were also observed. Since the choline hypothesis could possibly explain the beta-catenin mutations and tumour formation observed in the liver and kidney of mice, a worst case scenario could be to calculate a PDE 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 under same circumstances as in the mouse carcinogenicity study (Lehman-McKeeman et al., (2002) Toxicol. Sci. 67:38-45). Briefly, B6C3F1 mice were dosed dermally with diethanolamine in 95% ethanol for 4 weeks (5 days/week).The pattern of changes observed in choline metabolites after diethanolamine treatment was very similar to that observed in choline-deficient mice, and the NOEL for diethanolamine-induced changes in choline homeostasis was 10 mg/kg/day.

The lack of carcinogenicity in rats may be explained by use of a lower dose range in the carcinogenicity study and a lower dermal absorption of diethanolamine compared to mice leading to a lower systemic exposure to diethanolamine.

Taking into account that a non-genotoxic mechanism of carcinogenicity is postulated, a permissible daily exposure can be derived based on the NOAEL of the mice study fed a choline deficient diet in line with the method described in the Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA/CHMP/SWP/169430/2012).

The following uncertainty factors are applied:

F1: to account for extrapolation between species: 12

F2: to account for variability between individuals: 10

F3: to account for repeat-dose toxicity studies of short duration: 10

F4: applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity: 10

F5: may be applied if the no-effect level was not established: 1

F6: route to route extrapolation: 1

Overall uncertainty factor: 12000

PDE = 0,833 µg/kg bw per day

= 42 µg per day for a 50 kg person.

On the other hand, a PDE calculation based on the BMDL10 from the mouse carcinogenicity study (cfr CVMP referral AR EMA/275956/2021) can be performed as follows:

BMDL10 = 2.55 mg/kg

F1: 12

F2: 10

F3: 1

F4: 10

F5: 2 (BMDL10 to NOEL)

F6: 1

Uncertainty Factor: 2400

PDE = 1.06 µg/day

or 53 µg/50 kg person/day for life time treatment

This PDE approaches might represent an overly conservative approach taking into account that diethanolamine does not appear to penetrate human skin to any significant extent at concentrations relevant to human exposures from the use of personal care products.

In addition, in line with the recommendations of ICH M7 the PDE can be further refined to accommodate for less than lifetime exposure, e.g. 1-12 month dermal application. In this case the PDE should not exceed 705 µg/50 kg person/day.

3.1.2. Percutaneous penetration of diethanolamine

The percutaneous penetration of diethanolamine from consumer products (shampoos, hair dyes and body lotions) has been investigated by Kraeling et al. (2004). For this purpose, radiolabelled [^{14}C]-DEA was added to two commercial products from each class and applied to excised viable and non-viable human skin in flow-through diffusion cells. The products remained on the skin for 5, 30 and 24 h for shampoos, hair dyes and body lotions, respectively. After 24 h, most of the absorbed dose was found in skin: 2.8% for shampoos, 2.9% for hair dyes and 10.0% for body lotions. Only small amounts were absorbed into the receptor fluid: 0.08%, 0.09% and 0.9% for shampoos, hair dyes and body lotions, respectively. There was no significant difference in the absorption of DEA through viable and non-viable skin or from product application doses of 1, 2 or 3 mg lotion/cm^2. In 72 h daily repeat dose studies with a lotion, DEA appeared to accumulate in the skin (29.2%) with little diffusing out into the receptor fluid.

A subsequent study by Brain et al. (2005) confirmed similar levels of permeation through human skin of diethanolamine from cosmetic formulations. The permeability of diethanolamine through the skin of young children, the effects of elevated temperatures associated with bathing or showering or the effect of abrasions that alter skin integrity on the dermal absorption of diethanolamine has not been assessed.

3.1.3. The use of retention factors in regulatory framework for cosmetics

For cosmetics, the dermal route is often the most important one. In the frame of exposure assessment, the Scientific Committee on Consumers Safety (SCCS) has identified several exposure scenario's that comprise all the important functions and uses of a cosmetic ingredient. These include,

among others, the method of application (e.g. considerations whether the product is a rinse-off or leave-on product and which retention factor should be applied) and target consumer groups (e.g. children, people with sensitive, damaged or compromised skin) where specifically required.

The SCCS Notes of guidance for the testing of cosmetic ingredients and their safety evaluation (SCCS/1602/18) consider that with respect to dermal exposure, only a fraction of the product is retained on the skin. Therefore, a retention factor F_{ret} is used that represents the fraction available for uptake. For leave-on cosmetics (e.g. creams, body lotion, etc.) mostly a fraction of 1 (100%) is used, while for rinse-off cosmetics (e.g. shower gel, shampoo, hair conditioner, hair dyes, etc.) a smaller fraction is used that depends on the respective product. The retention factor is considered to be specific to the product category under consideration and not to depend on the substance itself (see Table 1). For products that are rinsed off directly after application, e.g. shower gel, hand soap and make-up remover, it is assumed that 10% will stay on the skin, whereas for non-rinse-off products a retention factor of 100% is assumed. In addition, in case of application to wet skin and taking into account the high water-solubility of the product (e.g. shower gel), a retention factor of 1% can be assumed. Hair products are assumed to be applied 90% to the hair and 10% to the scalp, so that their retention factor is set at 10%. Shampoo/hair conditioner is both a rinse-off and a hair product, so that its retention factor is considered to be 1% (10% of 10%) (SCCNFP, Notes of guidance for testing of cosmetic ingredients for their safety evaluation. 2000, Scientific Committee On Cosmetic Products And Non-Food Products Intended For Consumers). No measurement data are available to validate these retention factors (SCCS Notes of guidance for the testing of cosmetic ingredients and their safety evaluation 9th revision, 29 September 2015, SCCS/1564/15, revision of 25 April 2016) but they are generally accepted in the safety evaluation of cosmetic ingredients.

Table 1: Estimated daily exposure levels for different cosmetic product types according to Colipa (Cosmetic Europe) data (SCCNFP/0321/00, Hall et al. 2007, 2011).

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/day)	Retention factor [1]	Calculated daily exposure (g/day)	Calculated relative daily exposure (mg/kg bw/day)
Bathing, showering					
Shower gel	18.67 g	279.20	0.01	0.19	2.79
Hand wash soap [2]	20.00 g	-	0.01	0.20 [3]	3.33
Hair care					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner [2]	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74
Semi-permanent hair dyes (and lotions) [2]	35 ml (per application)	-	0.1	Not calculated	-
Oxidative/permanent hair dyes [2]	100 ml (per application)	-	0.1	Not calculated [4]	-
Skin care					
Body lotion	7.82 g	123.20	1.0	7.82	123.20
Face cream	1.54 g	24.14	1.0	1.54	24.14
Hand cream	2.16 g	32.70	1.0	2.16	32.70
Make-up					
Liquid foundation	0.51 g	7.90	1.0	0.51	7.90
Make-up remover [2]	5.00 g	-	0.1	0.50	8.33
Eye shadow [2]	0.02 g	-	1.0	0.02	0.33
Mascara [2]	0.025 g	-	1.0	0.025	0.42
Eyeliner [2]	0.005 g	-	1.0	0.005	0.08
Lipstick, lip salve	0.057 g	0.90	1.0	0.057	0.90
Deodorant					
Deodorant non-spray	1.50 g	22.08	1.0	1.50	22.08
Deodorant aerosol spray (ethanol-based) [5]	1.43 g	20.63	1.0	1.43	20.63
Deodorant spray (not ethanol-based)	0.69 g	10.00	1.0	0.69	10.00
Oral hygiene					
Toothpaste (adult)	2.75 g	43.29	0.05	0.138	2.16
Mouthwash	21.62 g	325.40	0.10	2.16	32.54

[1] The retention factor was introduced by the SCCNFP to take into account rinsing off and dilution of finished products by application on wet skin or hair (e.g. shower gels, shampoos, …) [SCCNFP/0321/00]
[2] Product types not covered by the Colipa (now Cosmetics Europe) studies: existing daily application amounts are divided by the mean human body weight of 60 kg.
[3] Danish Ministry of the Environment, Environmental Protection Agency: Survey of liquid hand soaps, including health and environmental assessments.
[4] Daily exposure value not calculated due to the low frequency of exposure (see also 3-8.3.1).
[5] Steiling et al. (publication in preparation); results presented to the SCCS. 'Ethanol-based' are products containing ethanol as principal ingredient.

External dermal exposure per day for a substance from a certain product category is calculated as follows:

$E_{dermal\ x} = C_x * Q_x * F_{ret\ x}$

$E_{dermal\ x}$ (mg/day): external exposure available for dermal uptake from product category x
X: product category
C_x (mg/g): concentration/ fraction of a substance in a product category x
Q_x (g/day): amount of product category that is applied/received per day
$F_{ret\ x}$: retention factor specific to product category x

The retention factor is a measure of how much of the product will be retained externally after use and thus defines the amount of the individual ingredient remaining on the skin before dermal penetration.

Dermal penetration depends on a number of factors including body part, skin type, product type, and chemical type. Api et al (2008) in their proposed quantitative risk assessment for fragrance ingredients point to the presence of irritating ingredients, penetration enhancers, etc. that can promote skin penetration. In addition, a description of use considerations impacting dermal absorption is provided (e.g. site of application, skin integrity that can be affected by e.g. shaving, atopic dermatitis). It is proposed that in the case of diethanolamine, a default conservative dermal penetration of 100% should be used for products applied to the skin. A such considerations regarding site of application and skin integrity are included in a worst-case default scenario.

3.2. Acceptability of using in medicinal products

Conclusion 1: Based upon the PDE calculations taking into account the results of the mice dermal carcinogenicity study and under the assumption that there is a non-genotoxic carcinogenic effect, human medicinal products for topical application should not contain more than 53 µg/day of diethanolamine in the case of life time treatment. In the case of a shorter application period up to 12 month 705 µg/day can be regarded as the PDE of diethanolamine. For medicinal products containing coconut oil diethanolamine condensate the level of contamination with diethanolamine should be identified and controlled at the PDE.

In parallel, it is recommended that marketing authorisation holders assess and justify whether the presence of diethanolamine in the concerned topically applied medicinal products is still justified.

Conclusion 2: Human medicinal products with dermal application containing diethanolamine should be formulated to avoid the formation of nitrosamines, e.g. not contain nitrate/nitrite at the same time in order to avoid any possibility of non-enzymatic conversion to N-Nitrosodiethanolamine (NDELA). This reaction is very unlikely for dermal products, since as a rule they do not possess an acidic pH as present in the stomach.

Conclusion 3: For rinse-off medicinal products containing diethanolamine a retention factor can be considered that takes into account rinsing off and in addition dilution following the recommended use of the medicinal product. More specifically, a retention factor of 0.01 is acceptable for rinse-off medicinal products containing diethanolamine such as shower gels, hand wash soap and shampoos/hair conditioners that are applied on wet skin or hair (diluted). For rinse-off medicinal products containing diethanolamine that are applied on dry skin or hair (undiluted), a retention factor of 0.1 is acceptable. The external dermal exposure per day should be calculated by multiplying the concentration of diethanolamine in the drug product (mg/g) with the amount of drug product that is applied per day (g/day) and the retention factor (0.01 or 0.1). The resulting external exposure is assumed to be 100% absorbed and as such applicable for all skin conditions and target patient groups (e.g. children, people with sensitive skin).

The application of these specific retention factors is acceptable only for risk assessments for diethanolamine-containing medicinal products.

List of references

Bachman AN, Kamendulis LM, Goodman JL (2006). Diethanolamine and Phenobarbital Produce an Altered Pattern of Methylation in GC-Rich Regions of DNA in B6C3F1 Mouse Hepatocytes Similar to That Resulting from Choline Deficiency. Toxicological Science, Vol. 90 (2), 317-325

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

Chandra M., Frith CH (1992) Spontaneous neoplasms in B6C3F1 mice. Toxicology Letters, Vol. 60 (1), 91-98

Dean, B.J., Brooks, T.M., Hodson-Walker, G., and Hutson, D.H. (1985). Genetic toxicology testing of 41 industrial chemicals. Mutat. Res. 153, 57-77.

EMA/CHMP/ CVMP/ SWP/169430/2012. Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

Hailey JR, Haseman JK, Bucher JR, Radvosky AE, Malarkey DE, Miller RT, Nyska A, Maronpot RR (1998). Impact of Heliobacter hepaticus infection in B6C3F1 mice from twelve National Toxicology Program two-year carcinogenesis studies. Toxicologic Pathology, Vol. 26 (5), 602-611

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5 (Suppl. 1), 3-142.

Hayashi SM, Ton TV, Hong HH (2003). Genetic alterations in the Catnb gene but not the H-ras gene in hepatocellular neoplasms and hepatoblastomas of B6C3F1 mice following exposure to diethanolamine for 2 years. Chemico- Biological Interactions, 146, 251-261

Keith MO and Tryphonas L. Choline lesions and the reversibility of renal lesions in rats. J Nutr. 1978;108:434-446

Konishi Y, Denda A, Kazuhiko U, Emi Y, Ura H, Yokode Y, Shiraiwa K, Tsutsumi M (1992). Chronic toxicity carcinogenicity studies of triethanolamine in B6C3F1 mice. Fundamental and Applied Toxicology, Vol. 18 (1) 25-29

Lachenmeier DW (2008). Safety evaluation of topical application of ethanol on the skin and inside the oral cavity. J. Occup. Med. Toxicol. 3:26.

Lehman-McKeeman LD, Gamsky EA (2000) Choline supplementation prevents diethanolamine-induced morphological transformation in Syrian hamster embryo cells: evidence for a carcinogenic mechanism. Toxicological Science, Vol. 55, 303-310

Lehman-McKeeman LD, Gamsky EA, Hicks SM, Vassallo JD, Mar MH, Zeisel SH (2002). Diethanolamine induces hepatic choline deficiency in mice. Toxicological Science, 67(1):38-45.

Lehman-McKeeman LD, Gamsky EA, Hicks SM, Vassallo JD, MH Mar, Zeisel SH. Diethanolamine Induces Hepatic Choline Deficiency in Mice. Toxicological Sciences, Volume 67, Issue 1, 1 May 2002, Pages 38–45

Mathews JM, Garner CE, Black SL, Matthews HB (1997). Diethanolamine absorption, metabolism and disposition in rat and mouse following oral, intravenous and dermal distribution. Xenobiotica, 27: 733-746.

Melnick RL, Mahler J, Bucher JR. 1994. Toxicity of diethanolamine. 2. Drinking water and topical application exposures in B6C3F1 mice. J Appl Toxicol, 14: 11-19

Munoz ER and Barnett BM (2003). Chromosome malsegregation induced by the rodent carcinogens acetamide, pyridine and diethanolamine in Drosophila melanogaster females. Mutat Res, 539; 137-144

NTP (1992). Technical Report on Toxicity Studies of Diethanolamine. NIH Publication No. 92-3343

NTP TR 478 (1999) Technical Report on the toxicology and carcinogenesis studies of Diethanolamine in F344/N rats and B6C3F1 mice (dermal studies), NIH Publication No. 99-3968

NTP TR 479 (2001) Technical Report on the toxicology and carcinogenesis studies of coconut oil acid diethanolamine condensate in F344/N rats and B6C3F1 mice (dermal studies), NIH Publication No. 01-3969

OECD. 2014. Test Guideline 489. In Vivo Mammalian Alkaline Comet Assay. In: OECD Guideline for the Testing of Chemicals. Paris, Organization for Economic Cooperation and Development.

Tsujiuchi T, Tsutsumi M, Sasaki T, Takahama M, Konishi Y. Different Frequencies and Patterns of β-Catenin Mutations in Hepatocellular Carcinomas Induced by N-Nitrosodiethylamine and a Choline-deficient L-Amino Acid-defined Diet in Rats. Cancer research 1999, 59

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA, Robert Safford (2008). Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol, 52(1):3-23.

Brain K.R., Walters KA, Green DM et al. (2005). Percutaneous penetration of diethanolamine through human skin in vitro: application from cosmetic vehicles. Food Chem Toxicol. 43:681-690.

Kraeling MEK, Yourick JJ & Bronaugh RL (2004). In vitro human skin penetration of diethanolamine. Food and chemical toxicology 42: 1553-1561.