Cosmetics Europe
the personal care association

DETERMINATION OF A SAFE LEVEL OF NDELA IN FINISHED COSMETIC PRODUCTS

Cosmetics Europe Industry Guidelines

DISCLAMER: *theses guidelines are intended to allow companies to respond to authorities in case they are challenged regarding NDELA level in finished cosmetic product. They are not intended to be shared externally nor directly with the authorities. They only provide a source for companies to engage with control authorities in case of question/concerns. The value mentioned for NDELA is* ***NOT*** *an absolute value and* ***can*** *be exceeded as long as the product is considered as safe. This paper is intended for informational only, and only for the use of the intended recipient(s). If the reader of this paper is not the intended recipient(s), please be on notice that you have received this paper in error and that any review, dissemination, distribution or copying of this paper is strictly prohibited. If you have received this paper in error, please delete this paper and notify the sender immediately.*

N-Nitrosodiethanolamine (NDELA) belongs to the class of compounds N-nitrosamines, not known to occur as natural products. These substances are formed essentially unintentionally and human exposure results from their presence in the environment as contaminants of a variety of products, such as cutting fluids and oils, certain pesticides, antifreeze, cosmetic products, tobacco and foods. N-Nitrosamines are usually readily formed if the necessary precursors, primarily secondary amines and nitrosating agents, are present. N-Nitrosamines contamination of cosmetics may be caused by contaminated ingredients or through the nitrosation of amines present in the finished product by nitrosating agents (*i.e.* in-situ formation of nitrosamines in the finished product). The formation of nitrosamines has been comprehensively reviewed by the Scientific Committee on Consumer Safety (SCCS 2011, 2012).

NDELA is the most commonly found N-nitrosamine in cosmetics (Schothorst and Somers, 2005; SCCS, 2011). Data on the occurrence of NDELA in cosmetic products in Europe is limited. Recent analytical surveys in the Netherlands have confirmed the presence of this compound in 25% of cosmetic products (which included shower gels, hair oils, shampoos and conditioners, cream and foam baths, mud baths, scrubs, soaps, and body washes). The range of concentrations was 23 to 992 µg/kg (Schothorst and Somers 2005). Another survey also reported the presence of NDELA in 28% of the tested products (mascara and eyeliners) at levels between 50 – 20000 µg/kg (NVWA,

2009). The SCCS (2012) has listed surveys conducted in Germany between 2007 and 2010 in which NDELA was detected in 39 of 450 cosmetic products tested.

The N-nitroso compounds are recognized as mutagenic carcinogens. The toxicity of NDELA has extensively been reviewed and evaluated (IARC, 2000). Based on sufficient evidence of carcinogenicity from studies in experimental animals (rats and hamsters), NDELA has been classified as carcinogenic by OEHHA Proposition 65; as possibly carcinogenic to humans (Group 2B) by IARC; as probable human carcinogen (Group B2) by the Environmental Protection Agency (EPA**)** and as **r**easonably anticipated to be human carcinogen by the National Toxicology Program (NTP). In Europe NDELA is classified as Category 1B carcinogen *i.e*. substances presumed to have carcinogenic potential for humans.

Nitrosamines including but not limited to NDELA, are prohibited in cosmetics in the EU (EU Cosmetic Products Regulation ((EC) No. 1223/2009), Annex II entry 410); in Canada (by Health Canada , 2011); in the USA (the FDA prohibits the use of nitrosamines as cosmetic ingredients). Regarding contamination of cosmetics with nitrosamines, the Agency issued a notice in the Federal Register in which stated that cosmetics containing nitrosamines may be considered adulterated and subject to enforcement action (Federal Register April 10 1979).

The State of California's Proposition 65 (Prop 65 - known officially as the Safe Drinking Water and Toxic Enforcement Act of 1986) has established a No Significant Risk Level (NSRL) for NDELA at 0.3 µg/day (OEHHA, 2013). NSRLs are "safe harbor levels" for carcinogens developed by California's EPA Office of Environmental Health Hazard Assessment (OEHHA). The NSRL is derived from a conservative scientific risk assessment that evaluates data from both animal studies and human epidemiological studies. The NSRL applies to an individual product and identifies the daily intake level of a chemical that is not expected to result in an increased incidence (measured over a lifetime of seventy years). Individual products marketed in the State of California must either comply with the NSRL or have specific labelling that identifies the product as containing a carcinogen.

At present a maximum permitted concentration for NDELA in cosmetics products has not been established in Europe. Annex II of the Cosmetic Products Regulation (2009) prohibits the presence of nitrosamines including NDELA in cosmetic products, and Annex III refers to a maximum limit of 50 µg nitrosamine/kg in relevant raw materials (i.e. fatty acid dialkylamides and dialkanolamides; monoalkylamines, monoalkanolamines and their salts; trialkylamines, trialkanolamines and their salts; and some hair dyes). This limit does not apply to finished products. Nevertheless, the European Cosmetic Product Regulation specifies in Article 17 that " The non-intended presence of a small quantity of a prohibited substance, stemming from impurities of natural or synthetic ingredients, the manufacturing process, storage, migration from packaging, which is technically

unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3[1]."

Regarding the technically unavoidable presence of nitrosamines. a Technical Report has been published at the ISO level: ISO/TR 14735 "Cosmetics – Analytical methods – Nitrosamines: technical guidance document for minimising and determining N-nitrosamines in cosmetics". The objective of this document was to provide advice on strategies to adopt in order to minimise the likelihood of nitrosamines formation in cosmetics, and to propose analytical approach for the analysis of these traces. This approach starts with screening by the Apparent Total Nitrosamine Content (ATNC) method. The ATNC method is known to give false positive results with several chemical species. So a positive result obtained with this method should always be confirmed by HPLC analyses of NDELA : HPLC post-column derivatization or/and HPLC-MS/MS methods (ISO 15819:2008, ISO 10130:2009). These 2 ISO Standards should therefore be the methods of choice, especially if discussions with regulatory authorities are likely."

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This approach was also supported by the SCCS in their opinion "opinion on nitrosamines and secondary amines in cosmetic products" SCCS/1458/11.

To complete the control of traces of nitrosamines in finished products, this had to be completed by a guidance on the safety level of such traces.

The aim of this safety assessment is the determination of a level for NDELA in finished cosmetic products that would pose a minimal health risk to the consumer.

- **Determination of a Toxicological Reference Value (TRV) for NDELA**

The routes of potential human exposure to NDELA are dermal contact, ingestion, and inhalation (HSDB 2013). Nitrosamines have been shown to be capable of penetrating the skin and numerous data are available in literature.

Percutaneous absorption studies in animals have shown that NDELA readily penetrated swine and monkey skin with a reported absorption of ~4 to 23% over 24 h (Marzulli et al, 1981) and up to 78%

[1] A cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use, taking account, in particular, of the following:
(a) presentation including conformity with Directive 87/357/EEC;
(b) labelling;
(c) instructions for use and disposal;
(d) any other indication or information provided by the responsible person defined in Article 4.

in the rat (Lijinsksy et al, 1981). In ECETOC report, in 1990, several studies have been reported and a skin absorption of 5% were taken into account for risk assessment according to results obtained in pig and through human skin.

Studies with excised human skin have also shown readily dermal penetration of NDELA. Franz et al (1993) reported that the total absorption at 48 hr ranged from approximately 35 to 65% of the dose applied, and was formulation dependent. The maximal skin absorption of 65% was obtained with the most lipophilic vehicle (isopropyl myristate). It is thus considered to be highly overestimated and it does not reflect what really occurs in cosmetic formula. Nevertheless, in shampoo base lotion and sunscreen cream, skin penetration has been also observed at a maximum of 60%.

In 2007 the SCCP (the Scientific Committee for Consumer Products (SCCP) now knows as the Scientific Committee for Consumer Safety) cited skin penetration to nitrosamines of 7.7% and 4.4% for leave on and rinse off products respectively which was used to calculate exposure rates to these compounds in children from bathing foam and shower gel. However, these data were obtained with N-dimethylnitrosamine and N-nitroso-N-methyldodecylamine and skin penetrations were significantly reduced by high permeant volatility (very low total recovery in these studies) and in the case of NDELA, no evaporative loss was evident. Thus the extrapolation of these values to NDELA is not relevant and the SCCP made no specific reference to the skin penetration of NDELA in its report of 2007.

Accordingly, a value of 60% for skin penetration of NDELA from cosmetic formulations is selected for calculation of exposure.

An exposure dose for NDELA in cosmetics representing a Lifetime Carcinogenic Risk (LCR) of 10^{-5} was calculated by the SCCS (2012) and can be considered as a level of NDELA in finished cosmetic products that poses a minimal health risk to the consumer.
This Exposure dose corresponds to the concentration of NDELA in cosmetics with a LCR less than 10^{-5} and can be back-calculated from the equation below:

LCR = Exposure dose / (HT25/0.25) where

HT25 = Human Dose Descriptor

HT25 (mg/kg bw/d) =T25/(bw human/bw animal [rat])$^{0.25}$

T25 = Animal Dose Descriptor (Chronic dose rate which will give tumours at specific tissue site in 25% of the animals)

For the quantitative risk assessment of carcinogens, the use of the dose descriptor T25, so called the "T25 method" (Sanner et al., 2001; Dybing et al. 1997), is the method used for quantitative risk

assessment of carcinogens in the EU (ECHA 2008; SCCS, 2012b and SCHER/SCCP/SCENIHR, 2009), and for setting specific concentration limits for non-threshold carcinogens (EC 1999).
Data from six carcinogenicity studies of NDELA in rats from which dose response information could be derived were used to determine an average dose descriptor T25 at 2.09 mg/kg bw/d, and subsequently the HT25 at 0.60 mg/kg bw/d for NDELA (SCCS, 2012).

The calculation of this exposure dose with these average dose descriptors is illustrated on the table below:

Exposure dose = LCR x HT25/0.25	
LCR (Lifetime Cancer Risk) 10^{-5}	10^{-5}
HT25 (mg/kg bw/d) (calculated using the formula HT25 = T25/(bw human/bw animal)$^{0.25}$)	0.6
T25 (mg/kg bw/d)	2.09
Exposure dose	24 ng/kg bw/day

This value of 24 ng/kg bw/day can be used as a Toxicological Reference Value (TRV) in human since this daily exposure to NDELA, is considered to pose a minimal health risk to the consumer.

- **Calculation of a maximum level of NDELA in finished cosmetic products that would pose a minimal health risk to the consumer**

- For the purpose of this assessment, dermal exposure is considered to be the most significant route of exposure from cosmetic products. Oral exposure occurs through products such as lipsticks, mouthwashes, and toothpastes. These products may be considered under a separate assessment.

- Data on the occurrence of NDELA in cosmetic products in Europe is limited, and the surveys conducted are not representative of all categories of cosmetic products. In the absence of solid data, or data on the categories of products that would/would not contain NDELA, a worst case scenario would be to assume for this assessment that all cosmetic products contain NDELA.

- The global daily exposure to cosmetic products of 15.1 g (A) used in this assessment is the sum of the calculated daily exposures for all cosmetic products through the dermal route and takes into consideration the corresponding retention factors as described on the SCCS latest Note of Guidance document (SCCS, 2016). This daily exposure was determined by a standard deterministic exposure assessment. This approach is likely a very conservative overestimation since it assumes that all

cosmetics used by dermal route are applied all together, every day over the lifetime. In the future, if a more realistic approach is recognized as valuable, this aggregated exposure assessment could be revised.

- The accepted default human body weight (bw) by the SCCS is 60 kg.

For the purpose of estimating a safe level of NDELA in finished cosmetic products, this assessment will use a maximum dermal absorption of 60%for NDELA, as determined by Franz et al (1993).

A safe level of NDELA in finished cosmetic products is calculated in accordance with the following formula (SCCP, 2006):

$$\textbf{SED} = \frac{\textbf{A} \times \textbf{C}\ (\%) \times \textbf{DAp}\ (\%)}{60\text{kg}}$$

Where:
SED (mg/kg bw/day) = Systemic Exposure Dose
A (g/day) = Estimated daily aggregate exposure to cosmetic products.
C (%) = the Concentration of the substance under study in the finished cosmetic product.
DAp (%) = Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real life conditions

$$\textbf{Accordingly, C (\%)} = \frac{\textbf{SED} \times 100 \times 100 \times 60}{(\textbf{A} \times \textbf{Dap})}$$

With	SED	= 24 ng/kg bw/day
	A	= 15.1 g/day i.e. $15.1*10^9$ ng/d
	DAp	= 60%

Estimated safe level of NDELA in finished cosmetic products = 0.000016% equating to 0.16 ppm (160 ppb)

- **Proposed Recommendation**

The likelihood of nitrosamines formation in cosmetics should be minimised and their presence be kept down to technically unavoidable presence, following the guidance provided in ISO/Technical Report TR 14735 “Cosmetics – Analytical methods – Nitrosamines: technical guidance document for minimising and determining N-nitrosamines in cosmetics”.

In all cases, on order to ensure safety of the product, trace levels of NDELA in finished cosmetic products, should be kept below a target level of less than or equal to 160 ppb.

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