

Scientific Committee for Consumer Safety (SCCS)
Request for an opinion on
NDELA in cosmetic products and nitrosamines in balloons

1. BACKGROUND

Nitrosamines are chemical compounds that may be present as contaminants in a number of products including food (such as certain beverages), tobacco products, rubber products and cosmetics. Some of these nitrosamines, such as N-nitrosodiethanolamine (NDELA) and N-nitrosodimethylamine (NDMA) are classified as category 1B carcinogens. Cosmetic products containing nitrosamines including NDELA are banned under the Cosmetics Directive¹ and its Annex III refers to the limit of 50 µg/kg for nitrosamines. Furthermore, limit values for nitrosamines and nitrosatable substances in toys were established in the new Toys Safety Directive² following an opinion of the Scientific Committee³, they enter into force on 20 July 2013.

Typically, when limit values are exceeded, cosmetics containing NDELA and balloons containing nitrosamines or nitrosatable substances are notified by Member State (MS) authorities to RAPEX⁴, since concentrations exceeding the limits are considered to pose a risk to human health. As an example, cosmetic products with 52 µg/kg to 56,750 µg/kg of NDELA were notified as posing serious risks.

However, not all authorities agreed to the classification of the risk as "serious". In one case a detailed risk assessment was provided concluding that the risk from 92 µg/kg NDELA in a shower gel was "negligible" (Annex I and Annex II). Also for nitrosamines in balloons such a divergence of risk classification was observed.

In order to resolve the above divergences, two Member State expert meetings were held in Brussels on 22 October 2009 (Annex III) and 27 January 2010 (Annex IV). They aimed at identifying the concentrations of NDELA in cosmetic products and nitrosamines in balloons that would differentiate between the risk levels "serious" and "less than serious".

Experts agreed that an additional lifetime cancer incidence of 1×10^{-6} should be used to differentiate between "serious" and "less than serious" risk for NDELA in cosmetic

¹ OJ L 768, 14.10.2008, p.1

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20080424:EN:PDF>
Entries 410 and 704 in Annex II of the Directive.

² OJ L 170, 30.06.2009, p.1

"Nitrosamines and nitrosatable substances shall be prohibited for use in toys intended for use by children under 36 months or in other toys intended to be placed in the mouth if the migration of the substances is equal to or higher than 0.05 mg/kg for nitrosamines and 1 mg/kg for nitrosatable substances."

³ SCCP Opinion on the Presence and Release of Nitrosamines and Nitrosatable Compounds from Rubber Balloons, 18 December 2007.

http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_121.pdf

⁴ Rapid alert system for non-food consumer products established under the General Product Safety Directive (GPSD).

products and for nitrosamines in balloons. Furthermore, an additional safety factor of 3 was agreed for children (Annex IV, draft summary report, not adopted yet). However there was no agreement on how the safety factor for children should be applied in the calculations: either by assuming a higher internal dose for children, or by setting a lower additional lifetime cancer incidence value, or by using some other method.

The calculations were based on the standard exposure values from the SCCP's Notes of Guidance for cosmetics safety evaluation⁵ and from the above mentioned SCCP's opinion on the release of nitrosamines from rubber in balloons. However, experts could not agree on how to calculate the so-called "Virtually Safe Dose" (VSD) which was necessary as an intermediate result.

Three different approaches to derive VSD were suggested by the experts:

- 1.1. The US-EPA in 1993⁶ derived an oral slope factor of 2.8 per 1 mg NDELA/kg body weight/day. This resulted in a VSD of 0.36 ng/kg bw/day. Some experts considered this VSD for NDELA inappropriate since it is lower than the VSD for NDMA which is known to be a stronger carcinogen. In addition, this kind of calculation uses a linearised multistage model as an extrapolation method, which was said to lead to very conservative estimates.
- 1.2. The VSD value for NDELA calculated with a Benchmark Dose Lower-confidence Limit (BMDL) of 10 was 3.6 ng/kg bw/day based on a 100 week rat study of Lijinski *et al.*⁷. Some experts pointed out the drawbacks of this study: Only two test concentrations were administered in the drinking-water for the rats, and only a limited number of rats (20-39 per group) were used. They considered the study as being of low quality and the VSD derived from it as not reliable.
- 1.3. Some experts proposed to take the VSD for NDMA and multiply it with 33 in order to extrapolate to the VSD of NDELA. The factor 33 is the factor between the TD50s of NDMA and NDELA in the rats study of Peto *et al.*^{8,9}. With such extrapolation the VSD for NDELA was 13.2 ng/kg bw/day. The experts considered the Peto *et al.* study of high quality due to its long duration and use of as many as 16 test concentrations to determine the dose-response relationship. Furthermore, the TD50s for NDMA and NDELA were in themselves central tendency estimates of the carcinogenic potency

⁵ http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_03j.pdf

⁶ US-EPA (1993). N-nitrosodimethylamine, carcinogenicity assessment. IRIS (Integrated Risk Information System), 2003; US Environmental Protection Agency, Washington DC, USA. Internet: <http://www.epa.gov/IRIS/subst/0252.htm>

⁷ Lijinsky W. and Kovatch R.M. (1985). Induction of liver tumors in rats by nitrosodiethanolamine at low doses. *Carcinogenesis* 6:1679-1681.

⁸ Peto, R., R. Gray, P. Brantom and P. Grasso. 1991a. Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study. *Cancer Res.* 51: 6415-6451.

⁹ Peto, R., R. Gray, P. Brantom and P. Grasso. 1991b. Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. *Cancer Res.* 51: 6452-6469.

and as such would be much more reliable than the VSDs (VSDs are way outside the visible range of tumour incidences). Thus the factor of 33 should be viewed as a reliable potency estimate of NDMA versus NDELA.

Annexes V and VI to this mandate show the above mentioned expert calculations.

2. TERMS OF REFERENCE

Against the above background, taking into account all relevant available scientific assessments, the SCCS is requested to:

- A) Assess if an additional lifetime cancer incidence of 1×10^{-6} is suitable as a practical approach to differentiate between the risk levels “serious” and “less than serious”;
- B) Assess which Virtually Safe Dose (VSD) values should be used for the calculations of NDELA concentrations in cosmetics and nitrosamines in balloons that correspond to an additional lifetime cancer incidence of 1×10^{-6} ;
- C) Assess if an additional safety factor of 3 is suitable for children and how it should be applied in the calculations;
- D) Calculate the concentrations of NDELA in cosmetics and nitrosamines in balloons which correspond to an additional lifetime cancer incidence of 1×10^{-6} both for adults and children.

3. DEADLINE

The SCCS's opinion would be appreciated by April 2011.