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Scientific Committee on Consumer Safety

SCCS

Opinion on
NDELA in Cosmetic Products and
Nitrosamines in Balloons

The SCCS adopted this opinion at its 15th plenary meeting

of 26 – 27 June 2012

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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http://ec.europa.eu/health/scientific_committees/consumer_safety/members_wg/index_en.htm

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This opinion has been subject to a commenting period of four weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged.
Revised opinions carry the date of revision.

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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 Directive[1] 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 Directive[2] following an opinion of the Scientific Committee[3]; 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 RAPEX[4], 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". 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 and 27 January 2010. 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 products and for nitrosamines in balloons. Furthermore, an additional safety factor of 3 was agreed for children (annex IV, draft summary report, not yet adopted). 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 evaluation[5] 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 the VSD were suggested by the experts:

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[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). http://ec.europa.eu/consumers/safety/rapex/index_en.htm

[5] The SCCP's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_03j.pdf

1.1 In 1993[6] the USEPA 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 N-nitrosodimethylamine (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 Lijinsky *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 by 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 rat studies 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 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.

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".

Are there other approaches that could provide a rationale for distinguishing between "serious" and "less than serious" risk?

B) For the three approaches mentioned in the background (1.1, 1.2, and 1.3) on the additional lifetime cancer incidence of 1×10^{-6}, assess which Virtually Safe Dose

[6] USEPA (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, Kovatch RM (1985). Induction of liver tumors in rats by nitrosodiethanolamine at low doses. Carcinogenesis; 6:1679-81.

[8] Peto, R., R. Gray, P. Brantom and P. Grasso. 1991a. Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or Nnitrosodimethylamine: 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 Nnitrosodimethylamine. Cancer Res. 51: 6452–6469

(VSD) values should be used for the calculations of NDELA concentrations in cosmetics and nitrosamines in balloons.

C) Assess, whatever the approach, if an additional safety factor(s) should be used for children and how it (they) should be applied in the calculations.

D) Calculate, for all approaches, the concentrations of NDELA in cosmetics and nitrosamines in balloons which differentiate between "serious" and "less than serious" risk.

3. INTRODUCTION

4. OPINION

4.1. Use of additional Lifetime Cancer Risk for risk assessment and risk management

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".

Are there other approaches that could provide a rationale for distinguishing between "serious" and "less than serious" risk?

The Scientific Committees (SCs, 2009 opinion on genotoxic carcinogens) concluded that risk assessment of compounds that are both genotoxic and carcinogenic should be done on a case by case basis. Whenever sufficient information is available, an appropriate dose descriptor, BMDL10 or T25, should be identified as a starting point to either apply linear extrapolation to determine an additional Lifetime Cancer Risk (LCR) or to calculate a Margin of Exposure (MoE), which represents the ratio between a dose descriptor and the estimated human exposure dose.
This is also in agreement with REACH (ECHA, 2008).

The EFSA Scientific Committee is of the view that in general "an MOE of 10,000 or higher, if it is based on the BMDL10 from an animal carcinogenicity study, would be of low concern from a public health point of view and might be considered as a low priority for risk management actions" EFSA 2005.

Recommendations have been issued by different organisations concerning acceptable/tolerable or less than serious LCR from exposure to environmental chemicals. The World Health Organisation (1993) recommends that the LCR for exposure to a carcinogenic contaminant in drinking water should be less than 10^{-5}. The US EPA as well as the US OSHA have a goal to reduce LCR from carcinogenic chemicals to less than 10^{-5}. Health Canada (2004) recommends a LCR of 10^{-5} for the purpose of assessing and managing of federal sites contaminated with carcinogenic substances. In the state of California, a warning is required when risks of 10^{-5} are exceeded for any agent listed as "known to the State to cause cancer" (Zeise et al., 1999). The REACH guidance on information requirements and chemical safety assessment (Chapter R.8: Characterization of dose [concentration]-response for human health, ECHA 2010) provides several examples and states that "based on experiences, cancer risk levels of 10^{-5} and 10^{-6} could be seen as indicative tolerable risk levels when setting DMELs (derived minimal effect levels) for workers and the general population, respectively". In addition, this guidance document provides example DMEL derivations for both LCRs, 10^{-5} and 10^{-6}. Finally, in the joint opinion on "Risk assessment methodologies and approaches for genotoxic and carcinogenic substances", the three scientific committees SCHER, SCCP and SCENHIR (2009) state that "the cancer risk decision points used for lifetime exposure of the general population are in general in the range of 10^{-5} and 10^{-6}".

It should be noted that in a population of 100 millions of the order of 500 000 (IARC 2008) persons are diagnosed with cancer every year. An LCR of 10^{-5} would result in 13 additional persons with cancer per year in case the whole population is exposed during its whole lifetime assuming an average lifetime of 75 years[10]. Whereas an LCR of 10^{-6} would represent 1.3 additional cancer case per year in a population of 100 millions (approximately 6.5 cancer cases per year in the 500 millions population on EU).
Due to the low sensitivity of epidemiological studies, calculated extra LCR of less than 10^{-3} can in general not be verified. In cases where high quality epidemiology and animal carcinogenicity studies are available, a good agreement was found between hazard assessment based on epidemiology and hazard assessment based on animal studies using the T25 method and a lifetime cancer risk of 10^{-3} (Sanner and Dybing, 2005). It is recognized, though, that linear extrapolation to very low levels may result in over or under estimation of risks at low exposures.

Conclusion
The SCCS is of the opinion that the decision between the risk levels "serious" and "less than serious" is in the end a risk management decision. However, the SCCS considers that an additional LCR of 1 x 10^{-5} or a MoE of 10 000 based on BMDL10 or a MoE of 25 000 based on T25 is suitable as a practical approach to differentiate between the risk levels. By using a LCR of 10^{-5} the cancer risk level from cosmetics representing a less than serious effect will be similar to the risk level considered to be of low priority in food (see section 4.4.3). To illustrate this practical approach, SCCS reiterates that in a population of 100 million of the order of 500 000 (IARC 2008) persons are diagnosed with cancer every year. An LCR of 10-5 would result in 13 additional persons with cancer per year in case the whole population is exposed during its whole lifetime assuming an average lifetime of 75 years. Whereas an LCR of 10-6 would represent 1.3 additional cancer case per year in a population of 100 million (approximately 6.5 cancer cases per year in the 500 million population on EU).

4.2. Approaches to the risk assessment of NDELA concentrations in cosmetics and nitrosamines in balloons

B) For the three approaches mentioned in the background (1.1, 1.2, and 1.3) on the additional lifetime cancer incidence of 1×10^{-6}, assess which Virtually Safe Dose (VSD) values should be used for the calculations of NDELA concentrations in cosmetics and nitrosamines in balloons.

The concept of a "Virtually Safe Dose" (VSD) was developed in response to difficulties in complying with the rigidness of the US Food, Drug and Cosmetic Act, which unconditionally banned food additives found to induce cancer at any dose level. In the context of the Delaney clause, a dose ("Virtually Safe Dose") was defined associated with 1 additional tumor/1 000 000 persons (LCR = 10^{-6}) through lifetime exposure. The LCR was calculated by dividing the dose descriptor TD50 (Sawyer et al., 1984) by 500 000 (linear interpolation) (Volokh, 1996). When no scaling factors were used for converting animal dose to human dose, the dose calculated to represent a risk of 10^{-6}, did actually, according to the methods used at present to calculate LCR, represent a risk of about 3.5 x 10^{-6} or 7 x 10^{-6}, if based on a rat or mice experiment, respectively (US EPA, 2005a, ECHA, 2008; SCs Scientific opinion on risk assessment methodologies and approaches for genotoxic and carcinogenic substances 2009; SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation 2010).

The three approaches mentioned in the terms of references are commented below

1.1 *The US-EPA in 1993 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.*

The calculation of US EPA (http://www.epa.gov/iris/) is based on the experiment of Lijinsky and Kovatch (1985). NDELA was administered in drinking water to F344 rats of both sexes at dose levels of 0, 28, and 64 mg/l for 100 weeks. The number of animals/sex/treatment group varied from 20 to 39. EPA did use the joint incidence of hepatocellular carcinomas and neoplastic nodule in females. US EPA calculated the animal daily dose to 0.88 and 2.01 mg/kg bw/d. It was calculated that an additional lifetime cancer risk of 10^{-6} for humans will represent a lifetime dose of 0.36 ng/kg bw/d using body surface for converting animal dose to human dose.
The SCCS considers the above EPA calculations are not in agreement with the state of art because the underlying study is not according to the present state of the art.

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 and Kovatch (1985). 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.

The SCCS notes that the above calculation was based on a linearised multistage model, and represents a LCR of 10^{-5}. The SCCS reiterates that the calculations are not in agreement with the state of art because the underlying study is not according to the present state of the art.

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. 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 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.

The SCCS points out that the rat studies of Peto et al (1991) were on NDMA and NDEA but not on NDELA.
The SCCS considers that with the number of studies available the risk assessment should be based on good quality experimental data of NDELA. The TD50 values used represent the mean of all rat studies on NDMA and NDELA considered in the Carcinogenic Potency Data Base (CPDB, http://potency.berkeley.edu/). The factor of 33 simply represents the ratio TD50 (NDELA) / TD50(NDMA (3.17 / 0.0959 = 33). The number 13.2 ng/kg bw/d represents 33 x 0.4 (daily lifetime dose of 0.36 ng/kg bw/d, as calculated in 1.1). The SCCS does not encourage such an approach.

Conclusion

The SCCS considers that none of the VSD values mentioned in the background (1.1, 1.2, and 1.3) are suitable for the risk assessment of NDELA in cosmetic products and nitrosamines in balloons. The SCCS has used state of the art methods to calculate LCR and MoE, see Section 4.4.1.

4.3. Need of an additional safety factor for children

C) Assess, whatever the approach, if an additional safety factor(s) should be used for children and how it (they) should be applied in the calculations.

Nitrosamines require metabolic activation by cytochromes P450s to alkylating intermediates to exert their carcinogenicity. The P450 enzyme 2E1 is suggested to be the major P450 contributing to the bioactivation of low molecular weight nitrosamines. The age-dependent development of P450 2E1 in liver has been described (Johnson et al. 2003). While the activity of 2E1 is only 20 % of adult activity in neonates, children between one and ten years only have slightly lower activities as compared to adults. For the other P450s, less relevant for nitrosamine metabolism, lower activities in children as compared to adults are described. These data suggest that the extent of bioactivation of nitrosamines in children between one and ten years will unlikely be higher as compared to adults, indicating that a specific safety factor for age-related differences in toxicokinetics is not required.

Regarding genotoxic carcinogens, US EPA (US EPA, 2005c) has suggested to use age dependent adjustments factors (ADAFs) in calculation of LCR in cases of exposure of children to carcinogens. Thus, it was suggested to use an ADAF = 10, during the first 2 years of life, ADAF = 3 for ages up to 16 years and ADAF = 1 for ages 16 until 70 years. This implies that if a LCR calculated in the usual manner(without taking a possible higher risk in relation to exposure of children into consideration) was 10^{-5}, the calculated risk for a lifetime of 70 years would increase to 1.6×10^{-5} if ADAF is used ([2 x 10 + 13 x 3 + 55 x 1] / 70 = 1.6). The SCCS is of the opinion that based on the variations between different carcinogenicity studies and the uncertainty in relation to low dose extrapolation the application of ADAFs represents a marginal effect and do not need be used in cases of exposure during the whole lifespan. However, when the exposure occurs only during childhood, the ADAFs should be applied unless it appears likely that children are not more sensitive than adults in relation to the agent involved.

Conclusion
On the basis of the above mentioned, the SCCS considers that no additional factor for risk assessment of nitrosamines for children is needed except for calculations when the exposure occurs only during childhood and data are available indicating that children have higher sensitivity as adults in relation to cancer risk.

4.4. Application of the MoE and LCR approach for risk assessment

D) Calculate, for all approaches, the concentrations of NDELA in cosmetics and nitrosamines in balloons which differentiate between "serious" and "less than serious" risk.

The following section describes the basic procedures and dose descriptors used in state-of-the-art risk assessment.

4.4.1. Dose descriptors used for risk assessment

Results from experimental animal studies with the same substance may show considerable variations. This may in part be due to differences in study design, experimental conditions, and the species and strains of animal used. However, even in cases where an experiment is repeated in the same laboratory under similar conditions, some variation in the results is in general found.

The T25

The T25 approach is defined as the chronic dose rate (usually expressed in units of mg per kg bodyweight per day) which will give tumours at a specific tissue site in 25% of the animals after correction for spontaneous incidence and within the standard life time of the species (Dybing et al., 1997). The T25 values are likely to be within the range of the experimental data. The use of data from the lowest dose giving a significant response should in most instances reduce the problem of intercurrent mortality to an acceptable degree, when e.g. calculating the TD50 value. It is recognized that the potential loss of precision does not match the order of magnitude differences in carcinogenic potencies found between high and low potency substances in animals.

In a study of 110 substances an almost perfect (slope in log-log plot of 1.05; correlation coefficient of 0.96) coincidence was found between potency estimates by the TD50 approach and the T25 method (Dybing et al., 1997). In another study a correlation coefficient of 0.94 was found when T25 and LED10 (the 95% lower confidence limit on a dose associated with 10% extra tumour risk adjusted for background) was compared for 68 substances (Sanner et al., 2001) It was concluded that, given the very large variation in carcinogenic potency between individual carcinogens, any difference between the T25 value and a "true" potency value should be negligible (Dybing et al., 1997).

The T25 method (Dybing et al., 1997, Sanner et al., 2001) has been used within the EU in setting specific concentration limits for carcinogens in preparations (EC 1999) and recently as a basis for calculation of LCR and for quantitative hazard assessment of non-threshold carcinogens in several regulatory areas e.g. ECHA (2008), SCCS (2010) and SCHER/SCCP/SCENIHR (2009).

The Benchmark Dose (BMD)

The BMD approach has been increasingly used and recommended (EFSA 2009, EFSA 2011, SCCS 2010, SCHER/SCCP/SCENIHR 2009). It is the dose level derived from the estimated dose-response curve associated with a specific change in the response defined through the Benchmark Response level (BMR). A BMR = 10% of extra risk over background has been set as a default level (EFSA 2009) when analysing cancer bioassays. The approach uses all available dose-response data from a study and fits a set of mathematical models. The lower one-sided confidence bound BMDL (denoted BMDL10 when setting BMR = 10%) accounts for the statistical uncertainty in the data (with the statistical certainty level of 95%) and is used as a Point of Departure (PoD), the Reference Point (RP) of the EFSA.

The TD50

The TD50 value was introduced primarily for ranking of carcinogens in the Carcinogenic Potency Database (CPDB), not for risk assessment and possible extrapolation to low doses. It is defined as the dose in mg/kg bw/d which, if administered chronically for the standard lifespan of the species, will halve the probability of remaining tumour free throughout that period; for details see Sawyer et al. (1984). The determination of the TD50 value is complicated by intercurrent deaths due to causes other than tumorigenesis and the non-observability of the time of onset (Portier and Hoel 1987).

The Slope Factor (SF)

The slope factor has been used by the USEPA as a convenient descriptor of cancer potency (see http://www.epa.gov/iris/carcino.htm) characterising the slope of the dose-response curve at low doses (where the slope is still linear). It has dimensions of risk of

cancer per unit dose and converts estimated daily intakes averaged over a lifetime of exposure directly to incremental risk of an individual developing cancer. Since the SF characterises the slope of the dose-response curve at low doses by a linear approximation, it is a specific modification of a model class (the linearised multistage model) also used in the BMD approach.

Further approaches are described in the SCCS Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, SCCS/1458/11.

For better comparison with BMDL10, the SCCS decided to normalise the dose descriptors to the 10% level (i.e. using T25/2.5 and TD50/5 in the assessment of nitrosamines) as shown in table 1.

Table 1 Dose descriptors used in the assessment of nitrosamines based on carcinogenicity studies on rats, applying three different methods to define a common PoD. The data are taken from the calculations presented in the Opinion on Nitrosamines and Secondary Amines in Cosmetic Products SCCS/ 1458/11, and normalised to the 10% level (T25/2.5 and TD50/5) to make it easier to compare the results.

Name	T25-method (mg/kg bw/d) (range)	BMDL10 (mg/kg bw/d)	TD50-method (mg/kg bw/d)
N-nitrosodimethylamine (NDMA)	0.023 (0.013-0.044)	0.027	0.019[m,v]
N-nitrosodiethylamine (NDEA)	0.034 (0.0035-0.076)	0.018	0.0053[m,v,t]
N-nitrosomorpholine (NMOR)	0.038 (0.019-0.049)	0.7	0.022[m]
N-nitrosodibutylamine (NDBA)	0.15	NA	0.14
N-nitrosodiethanolamine (NDELA)	0.84 (0.42-1.28)	0.73	0.63 [m,v]

Notes: NA not available.

[m] There is more than one positive experiment.

[v] Variation is greater than 10-fold among statistically significant (two-taled $p<0.1$) TD50 values from different positive experiments.

[t] TD50-method based on the same data as T25 was 0.032 mg/kg bw/d.

Conclusion

The SCCS concluded that the BMDL10 from the BMD approach and the T25 approach are two dose descriptors which can be used to characterise the risk of NDELA in cosmetics and of nitrosamines in balloons. TD50 is considered less suitable for the above mentioned reasons

4.4.2. Extrapolation to humans

Since most carcinogenicity studies are performed in animals, an extrapolation between species, i.e. from animals to humans is required. For oral exposures, an allometric scaling was used where the administered doses are adjusted with body weights to the power of ¾ (ECHA 2008, SCCS 2010, SCHER/SCENIHR/SCCS 2009, USEPA 2005a) based

on allometric scaling. The adjustment factors "f" are derived from the body weights (bw) according to the formula:

$$f = (bw_{human}/bw_{animal}) / (bw_{human}/bw_{animal})^{3/4} = (bw_{human}/bw_{animal})^{1/4}$$

The adjusted T25 (HT25) is obtained from the formula:

$$HT25 = T25/(bw_{human}/bw_{animal})^{0.25}$$

Therefore, if the animal dose is expressed in mg/kg bw_{animal}/d, the equivalent human dose, given in /kg bw_{human}/d (assuming a body weight of 60 kg), is smaller by a factor of f = 6.7 when using data from male mice (weight of 30 grams) and of f = 3.3 when using data from male rats (weight of 500 grams), respectively.

It is to be noted that allometric scaling should not be applied if the effects do not depend on metabolic rate or systemic absorption, e.g. in the case of local effects.

4.4.3. Calculation of LCR and MoE

LCR

A number of mathematical models have been developed for extrapolation from responses at the high experimental doses generally used in animal carcinogenicity bioassays to those at the substantially lower exposure levels usually encountered in human situations, well outside the range of experimental observations. The most extensively used mathematical model for calculation of a LCR has been the so-called Linearised Multistage (LMS) model (USEPA 1986b). USEPA (1996, 2005a) has more recently proposed to use linear extrapolation downwards from a benchmark dose referred to as LED10 (the 95% lower confidence limit on a dose associated with 10% extra tumour risk adjusted for background, equivalent to a BMDL10). As pointed out above, in the EU the use of T25 and linear extrapolation is recommended. It should be noted that the results obtained with these three methods (LMS, LED10, T25) are very similar (Sanner et al. 2001). A LCR can be calculated from HT25 if the exposure dose, denoted EXP, is known from the formula:

$$LCR = \frac{\text{Exposure dose}}{\text{HT25}/0.25}$$

MoE

The Margin of Exposure (MoE) is considered to be a practical approach for the formulation of advice to risk management. It takes into account both the human exposure data and the Point of Departure (PoD) (the Reference Point (RP) of the EFSA) derived from available dose–response data for the most critical endpoint without extrapolation to the substantially lower exposure levels usually encountered in human situations. It allows, in particular, comparison between compounds to support prioritization for risk management action (Barlow et al. 2006). Key points to consider in conducting a MoE assessment were also compiled by Benford et al. (2010a, 2010b 2010c). The MoE is numerically defined as the ratio of the Point of Departure (PoD) of the critical effect to the theoretical, predicted, or estimated exposure level (WHO 2009). The magnitude of the MoE gives an indication of the level of concern, but is not a

numerical quantification of risk; the larger the MoE, the smaller the potential risk posed by exposure to the substance under consideration. The EFSA Scientific Committee considered that a MoE of 10,000 or more, based on animal cancer bioassay data, would be of low concern, see EFSA (2005). It was concluded that a difference between the reference point and human intakes of at least 100 would be sufficient to allow for these inter- and intraspecies differences. An additional 100-fold difference would allow for the additional uncertainties covered under inter-individual human variability in cell cycle control and DNA repair, and for missing knowledge on the dose effect relationship below the reference point (RP), and whether at dose levels below that point cancer incidence is increased and that it cannot be regarded as a surrogate for a threshold in the case of a substance that is both genotoxic and carcinogenic.

A MoE higher than 10,000 based on BMDL10 can, in cases of lifelong exposure, be associated with a LCR lower than 3.5×10^{-5} if based on a male rat experiment and lower than 7×10^{-5} if based on a male mice experiment and using linear extrapolation (ECHA 2008, USEPA 2005a). However, linear extrapolation using the MoE approach has not been recommended to derive a risk estimate or a level of actual risk in the exposed population (Barlow et al. 2006).

4.4.4. NDELA in cosmetics

4.4.4.1. Risk assessment of NDELA in cosmetics

The SCCS identified six studies form which dose-response information on NDELA in animals could be derived: Berger et al. (1990), Hecht et al. (1989), Lijinsky et al. (1984b), Lijinsky and Kovatch (1985), Preussman et al. (1982) and Zerban et al. (1988), see annex I.I.

For the risk assessment of NDELA, the dose descriptors T25 and BMDL10 have been determined on the basis of the available data from these carcinogenicity studies on experimental animals (see annex I). TD50-values are reported for reasons of comparison below, but were not used to calculate the LCR or the MoE, see table 1.

The T25 could be calculated for each of the six rat studies and a range of T25 values between 1.05 and 3.21 was obtained. The mean T25 of 2.09 mg/kg bw/d corresponding to a human HT25 of 0.60 mg/kg bw/d was chosen as the PoD.

An exposure dose of 24 ng/kg bw/d representing a LCR of 10^{-5} was calculated from the HT25 value of 0.60 mg/kg bw/d using the formula described in section 4.4.2 (see SCCS Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, SCCS/1458/11.). Thus, exposures of NDELA < 24 ng/kg bw/d translate into LCRs < 10^{-5}.

The SCCS calculated the MoE based on the BMDL10 = 0.73 mg/kg bw/d (see table 1) derived from a combined evaluation of the data sets of two high quality studies (Berger et al. 1987, Berger et al. 1990, Preussmann et al. 1982), see annex I.I.

4.4.4.2. Calculation of the MoE and LCR for NDELA in cosmetics

The SCCS used a contamination of 50 µg NDELA/kg, as currently regulated in the Cosmetic Directive for raw materials, for the MoE and LCR calculations. This reflects a highly unrealistic worst case scenario where all raw materials would be contaminated at that level. The frequency and levels of contamination of cosmetic products from the European market, analysed since the year 2000 are given in annex III.

Table 2 MoE and LCR calculations based on the assumed occurrence of NDELA in cosmetic product examples at 50 µg/kg (50 ppb = 50 ng/g).

	Mascara	Shower gel	Handwash soap	Body lotion

Frequency of application[1)]	2/day	1.43/day	10/day	2.28/day
Estimated daily amount applied[1)]	0.025 g	18.67 g	20.00 g	7.82 g
Retention factor[1)]	1.0	0.01	0.01	1.0
Dermal absorption for NDELA[2)]	**65%**	**65%**	**65%**	**65%**
Body weight	60 kg			
SED (Systemic Exposure Dose)[1)]	50 ng/g × 0.025 g × **0.65** / 60 kg 0.014 ng/kg bw/d	50 ng/g × 0.19 g × **0.65** / 60 kg 0.1 ng/kg bw/d	50 ng/g × 0.20 g × **0.65** / 60 kg 0.11 ng/kg bw/d	50 ng/g × 7.82 g × **0.65** / 60kg 4.23 ng/kg bw/d
BMDL10 T25/HT25	0.73 mg/kg bw/d 2.09/0.60 mg/kg bw/d			
MoE (BMDL10 based)	**$5.2\ 10^7$**	**$7.3\ 10^6$**	**$6.6\ 10^6$**	**$1.7\ 10^5$**
LCR	**$< 10^{-5}$** (0.0006×10^{-5})	**$< 10^{-5}$** (0.005×10^{-5})	**$< 10^{-5}$** (0.005×10^{-5})	**$< 10^{-5}$** (0.2×10^{-5})

Notes: [1)] SCCS's Notes of Guidance for the testing of cosmetic ingredients and their Safety Evaluation, 7th revision (2010);

[2)] Franz et al. (1993).

Therefore, a contamination of 50 µg NDELA/kg is associated with a MoE > 10,000 in all four of the cosmetic products considered when using the BMDL10 as PoD and the LCR calculated using the T25 is less than 10^{-5}.

4.4.4.3. NDELA concentrations in cosmetics associated with a MoE of 10,000 and with a LCR < 10^{-5}

As mentioned in section 4.1, a MoE of 10,000 or higher based on BMDL10, or of 25,000 or higher based on T25 is considered by the EFSA to be of low concern.

As a pragmatic approach, the concentration of NDELA in cosmetics corresponding to a MoE greater than 10,000 or a LCR less than 10^{-5} may be back-calculated from the Point of Departure (PoD) (i.e. the BMDL10 or the T25). However, the SCCS emphasises that this is not an agreed approach in cancer risk assessment and that these levels merely provide information on product specific contamination levels connected to a MoE of 10,000, assuming life time exposure and they do not provide distinction between safe and non-safe contamination levels.

Accordingly, the exposure to a cosmetic product (as described in the Notes of Guidance) with a retention factor of 1 (body lotion), requires that the NDELA contamination in this product should not exceed 0.86 mg/kg, equivalent to a Systemic Exposure Dose (SED) of 73 ng/kg bw/d. Similar calculations (MoE of 10,000 resulting in a SED of 73 ng/kg bw/d) for other products from table 2 would result in a maximum NDELA contamination of: 269.5 mg/kg in mascara; 35.5 mg/kg in shower gel; and 33.7 mg/kg in handwash soap (see SCCS Notes of Guidance 2010). The above calculations are based on the BMDL10 of 0.73 mg/kg bw/d. A calculation based on HT25, equal to 0.60 mg/kg bw/d, allows for a

LCR of < 10^{-5} and corresponds when the SED is < 24 ng/kg bw/d. For body lotion this will require that the NDELA contamination should not exceed 0.28 mg/kg.

Mitigation measures against nitrosamine contamination in cosmetic products have been discussed in the SCCS Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, SCCS/1458/11.

"As currently regulated, the purity specification of 50 µg nitrosamine/kg should apply to raw materials and to all nitrosamines potentially formed. This limit (50 µg nitrosamine/kg) does not apply to finished products. The secondary amine content in the finished product determines the content of nitrosamines potentially formed. The secondary amine content in raw materials should be as low as achievable, following GMP rules, but should not exceed the limits as laid down in the Directive. The SCCS supports the present regulation since it provides a high degree of consumer protection."

4.4.5. Nitrosamines in balloons

4.4.5.1. Point of departure of NDMA, NDEA, NDBA, NMOR

The four nitrosamines most commonly found in balloons are: N-nitrosodiethylamine NDEA (CAS No. 55-18-5); N-nitrosodimethylamine NDMA (CAS No. 62-75-9); N-nitrosomorpholine NMOR (CAS No. 59-89-2); and N-nitrosodibutylamine NDBA (CAS No. 924-16-3). For each of these substances, the BMD and the T25 have been calculated (for the calculations of T25 and the corresponding HT25 the values are given as the mean ± SD) and are given in the SCCS Opinion on Nitrosamines and Secondary Amines in Cosmetic Products (SCCS/1458/11).

NDMA

Dose-response information on NDMA in animals was obtained from: Arai et al. (1979), Lijinsky and Reuber (1984a), Lijinsky et al. (1987), Peto et al. 1991 and Terao et al. (1978).

For NDMA the study with highest quality was that of Peto et al. (1991a/b) where the male rat was the most sensitive strain with a BMDL10 = 0.027 mg/kg bw/d.

T25 = 0.058 ± 0.028 mg/kg bw/d; HT25 = 0.016 ± 0.008 mg/kg bw/d (based on seven experiments).

NDEA

Dose-response information on NDEA in animals was obtained from: Berger et al. (1990), Druckrey et al. (1963), Habs et al. (1980), Lijinsky et al. (1981), Lijinsky et al. (1983) and Peto et al. (1991a/b).

For NDEA three high quality studies were available. In the Peto et al. (1991a/b) study the most sensitive animals were male rats with a BMDL10 = 0.018 mg/kg/day.

T25 = 0.085 ± 0.065 mg/kg bw/d; HT25 = 0.024 ± 0.019 mg/kg bw/d (based on seven experiments).

NDBA

Two studies were identified for N-nitrosodibutylamine (NDBA) (see also USEPA IRIS: http://www.epa.gov/iris/subst/0037.htm) from which dose-response information on N-nitrosodibutylamine (NDBA) in animals was available (Bertram and Craig 1970, Druckrey et al. 1967). From this study, a BMDL = 2.0 mg/kg/d was calculated for NDBA. However, it needs to be taken into consideration that the dose range selected is of influence to organ specific tumor induction and that lower NDBA doses still may have caused tumor

formation in organs such as the urinary bladder. Butyl-3-carboxypropyl-nitrosamine, the NDBA metabolite responsible for bladder cancer induction is considered to be a potent carcinogen (Irving et al. 1984, Janzowski et al. 1994). Furthermore, Druckrey et al. (1967) provide only limited information on the total number of animals per dose group in this study which adds additional uncertainty to the BMDL10 value.

Bertram and Craig (1970) exposed 50 male and female C57Bl6 mice to either 60 mg or 240 mg dibutylnitrosamine/L in drinking water. This resulted in squamous-cell carcinomas of the bladder in 44/90 for the high-dose mice and 19/89 for the low-dose mice. However this study was not suitable for a BMD analysis.

T25 = 0.37 mg/kg bw/d; HT25 = 0.11 mg/kg bw/d (based on one experiment, see annex II).

NMOR

Dose-response information on NMOR in animals was obtained from: Hecht et al. (1989), Lijinsky and Reuber (1982) and Lijinsky et al. (1988).. The SCCS derived a BMDL10 value of 1.7 mg/L from these data. However, when using the conversion indicated in the publication, a BMDL10 of 0.7 mg/kg bw/d was derived.

T25 = 0.094 ± 0.036 mg/kg bw/d; HT25 = 0.025 ± 0.009 mg/kg bw/d (based on four experiments).

4.4.5.2. Calculation of the MoE and LCR for nitrosamines in balloons

The following exposure models for nitrosamines from balloons are taken from the SCCP Opinion on the Presence and Release of Nitrosamines and Nitrosatable Compounds from Rubber Balloons (SCCP/1132/07), which are based on exposure models used by RIVM and by BfR. In the present opinion only nitrosamines have been considered; the potentially nitrosatable precursors have not been considered.

(taken from SCCP/1132/07)

Exposure model used in the RIVM approach

1. *Of the test results described in KvW report ND1TOY01/01, the total migration numbers of all nitrosamines and of all nitrosatable precursors together were used.*
2. *The mean migration of nitrosamines and precursors from balloons was measured to be 0.13 and 1.51 mg/kg product/hour, respectively, with the respective maximum migration 0.63 and 5.73 mg/kg product/hour.*
3. *For exposure of children to nitrosamines through contact with balloons, it was assumed that children may lick the surface of an inflated balloon (with a surface of 10 × 10 = 100 cm^2) or suck the mouthpiece of a balloon for a period of one hour, 5 times per year.*
4. *The average weight of a mouthpiece and of 100 cm^2 inflated balloon was determined to be 270 mg and 90 mg, respectively.*
5. *The maximum exposure of children to nitrosamines during one hour was calculated by multiplying maximum migration levels × weight of the mouthpiece (0.63 × 270 = 170 ng/ hr). Per year, this maximum exposure to nitrosamines is 5 x 0.63 × 270 = 850 ng/year.*
6. *The maximum exposure to nitrosatable substances was calculated in the same way and was 5.73 × 270 = 1,547 ng/hr and 7,735 ng/year.*
7. *Subsequently, RIVM compared the calculated exposure with the VSD or Risk Specific Dose (RSD) corresponding to a LCR of 10^{-6}. Based on animal experiments, the RSD*

for NDMA was 1.5 ng/kg body weight per day. For children in the age of 3 (to 10 years) with a mean body weight of 15 (to 30) kg, this corresponds to a RSD of 22 (to 45) ng/day = 8.000 (to 16.0000) ng/year for NDMA.

8. *The highest cumulated annual exposure to NDMA by contact with the mouthpiece (850 ng/year) is 10 (to 20) times lower than the RSD cumulated over 1 year.*
9. *When it is assumed that 1% of all precursors will be converted in vivo into nitrosamines (Van Leeuwen et al. 2003), the cumulated exposure to nitrosamines and precursors is maximal 5 × (170 + (1% × 1547) = 5 × 185 = 925 ng/year.*
10. *The highest exposure to nitrosamines and nitrosatable substances together due to contact with the mouthpiece is still about 10 (-20) times lower than the RSD of 8.000 (–16.000) ng cumulated over 1 year.*

Thus the LCR risk from exposure to nitrosamines and nitrosatable substances from rubber balloons is considered to be negligible. In addition, it was concluded that the mean exposure of 35 ng/h (= 0.13 × 270) for a single one-hour period is similar to the amount that children may ingest every day, without exceeding an additional cancer risk of 1:10^6.

BfR approach

In this assessment the following assumptions were made (BfR 2003).

1. *Exposure was assessed as a worst case scenario on the basis of the maximum migrated quantities measured for individual N-nitrosamines.*
2. *A surface area approach was adopted, assuming that one kilogram of uninflated balloon material corresponds to an area of 4 m^2.*
3. *The exposure surface of a balloon in use is assumed to be 10 cm^2.*
4. *When the levels of table 3 are taken, a maximum ingestion quantity of 0.155 µg NDMA, and 0.158 µg total nitrosamines per day is calculated.*

Table 3 Maximum migration rates and exposures as measured in Germany (BfR 2003)

	N-nitrosamines			**Nitrosatable substances**		
	Maximum migrated		**Ingestion from**	**Maximum migrated**		**Ingestion from**
	mg/kg	**µg/dm²**	**µg/10 cm²**	**mg/kg**	**µg/dm²**	**µg/10 cm²**
NDMA	0.62	1.55	**0.155**	2.82	7.05	0.705
NDEA	0.07	0.18	0.018	2.26	5.65	0.565
NDBA	0.47	1.18	0.118	4.73	11.83	1.183
NDBzA	0.06	0.15	0.015	0.66	1.65	0.165
NDiNA	0.19	0.48	0.048	0.18	0.45	0.045
NDiDA	0.04	0.10	0.010	0.60	1.50	0.150
NDMOR	0.01	0.03	0.003	-	-	-
Product*	0.63	1.58	0.158	5.73	14.33	1.433

** Maximum quantity of N-nitrosamines and nitrosatable substances in a balloon migrated in one hour. Depending on the vulcanisation accelerator used, nitrosamines and precursors migrated in various combinations and quantities. The maximum quantity in the product therefore does not correspond to the sum of the maximum migrated quantities of individual N-nitrosamines and their precursors.*

This calculated worst-case intake is of the same order of magnitude as ingestion from foodstuffs (0.2 µg N-nitrosamines per day for women and 0.3 µg for men). However, unlike foodstuffs, N-nitrosamines in balloons are not ingested on a regular basis: exposure of consumers is only occasional and the estimated quantity ingested is based on a worst-case scenario. BfR thus considers that in general, there is no serious health hazard.

However, it becomes clear from these and previous migration studies that substantial quantities of N-nitrosamines and nitrosatable substances can rapidly migrate from balloons. Also dynamic processes, as in the sucking of balloons, seem to favour migration. BgVV/BfR considers that balloons for which the N-nitrosamine level exceeds 400 µg/ kg infringe the Toys Safety Ordinance and are a potential health hazard. This amount is derived from the limit on teats and soothers, i.e. 10 µg/kg and 100 µg/kg per hour for the migration of nitrosamines and nitrosatable substances, respectively. If it is assumed that a soother weighs 10 grams (g), then a maximum of 0.1 µg of nitrosamines and 1 µg of nitrosatable substances could be ingested. If the same requirements are applied to balloons and exposure by surface area is presumed, this results in a maximum value of 400 µg of nitrosamines and 4 milligrams (mg) of nitrosatable substances per kg of balloon mass, assuming that a child sucks a surface of 10 square centimetres (cm²) and that a surface of 4m² corresponds to a balloon mass of 1 kg.

Comparison of the two assessment strategies

When the two different risk assessments of RIVM (2003) and BgVV/BfR (2002, 2003, and 2004) are compared, one of the most striking differences is the fact that RIVM is calculating an average risk based on mean migration levels and spread out over one year, while BfR is more focused on exposure to balloons with extreme nitrosamine levels (peak exposures). Furthermore, different assumptions have been made for calculating the risk; these are summarised in table 4.

Table 4 Parameters used and assumptions made for the risk assessment of nitrosamines in balloons by RIVM and BfR, taken from the SCCP Opinion (SCCP/1132/07)

	RIVM	**BfR**
Mean migration level (mg/kg/hr)	Nitrosamines: 0.13 Precursors: 1.51	
Maximum migration level (mg/kg/hr)	Nitrosamines: 0.63 Precursors: 5.73	NDMA: 0.62 Nitrosamines: 0.63
Exposure rate/year	5×1 hour	
Surface area	100 cm2	10 cm^2
Weight of balloon	Surface: 90 mg Mouthpiece: 270 mg	
Conversion of precursors to nitrosamines	1%	
Dose associated with risk of 1×10^6	1.5 ng/kg bw/d	
Weight of exposed children	15-30 kg	
Surface area approach		1 kg balloon corresponds to 400 dm^2
Worst case scenario		100% of nitrosamines is ingested

Another difference is the surface area approach of BfR, while RIVM takes the weight of the licked surface of 100 cm^2 inflated balloon or the weight of the mouthpiece. However, when both strategies are compared, the calculated levels of nitrosamine intake are of the same order of magnitude. For average exposure, BfR agrees with RIVM that there is no serious health hazard. Balloons with a mean migration level of 0.13 mg/kg/hr result in an exposure of 35 ng/day (0.13 × 270), a value that lies around the RSD of 22-45 ng/day. However, BfR is more concerned with the peak exposures that can occur by licking a balloon with extremely high levels of nitrosamines, a scenario that is not considered by RIVM. Calculation of exposure based on RIVM assumptions, with the maximum migration level for nitrosamines leads to a level of 0.63 (mg/kg maximum nitrosamine migration from balloons) × 270 (mg, mouthpiece) = 170 ng/day, a level that is comparable to the 158 ng/day found by BfR using their surface area approach. This level exceeds the above mentioned RSD by a factor 4 to 8.

Comment

The SCCS considers that there are uncertainties in the two exposure models i.e. frequency of use, duration of use, lifetime period of exposure and contact area. For a reliable exposure assessment, these parameters should be determined. Alternatively, biomarkers of nitrosamine exposure may be considered for future exposure assessments.

The SCCS bases the risk characterisation on the two exposure models described above. More recent data on occurrence of nitrosamines in balloons from the German market demonstrate that between 2005 and 2010, no major changes in contamination levels were observed (Jahresbericht 2010). Of note, in 2008 about 80% (see figure 1) of the balloons tested were <10 µg/kg nitrosamines but this was not continued in the following years.

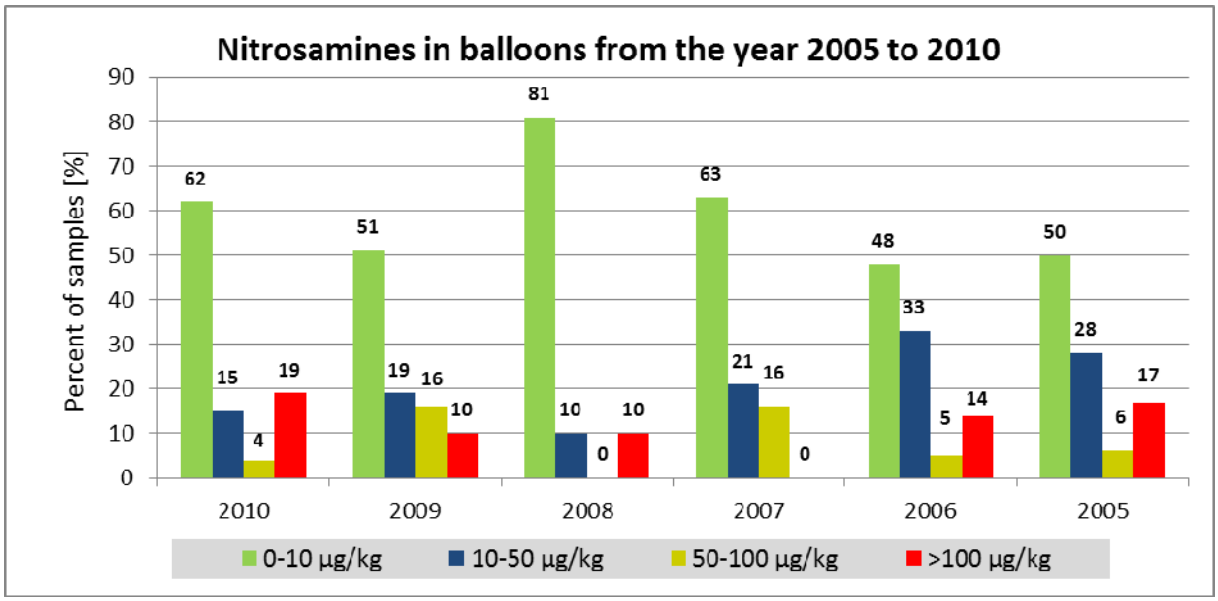

Figure 1 Nitrosamines in balloons from the German market 2005-2010 (Jahresbericht 2010, Food Surveillance Baden-Württemberg, Germany).

MoE calculation based on BfR evaluation

According to the BfR (Bewertung von Nitrosaminen in Luftballons, Ergänzende Stellungnahme 26.04.2004) 1 kg of balloon corresponds to 400 dm^2 (i.e. 4 m^2 or 40,000 cm^2). It is assumed that a 3 year old child of 15 kg body weight chews/sucks an area of

10 cm^2. These materials may contain NDMA, NDEA, NDBA and NMOR (Altkofer et al. 2005). For calculation of the MoE, the BMDL10 of NDEA (18 µg/kg bw/d) is taken as a conservative approach because NDEA has the lowest BMDL10 value, representing the most potent and best investigated nitrosamine.

Exposure = 10 (cm^2, balloon)* 50 (µg/kg nitrosamine content)/40,000 cm^2 = 12.5 ng/d.

For a 3 year old child of 15 kg, the resulting exposure would be 0.83 ng/kg bw/d at an assumed NDEA contamination of 50 µg/kg rubber.

The resulting MoE, based on a BMDL10 for NDEA of 18 µg/kg bw/d (see table 1), has a value of 21,000 (21,688 rounded to the lower value with two significant figures).

The LCR calculation is based on the same exposure as for the MoE calculation, since the T25 of NDMA, NDEA and NMOR, the most potent nitrosamines (see SCCS Opinion on Nitrosamines and secondary Amines, SCCS/ 1458/11;table 3), are very close to each other.

The SCCS decided to use the average HT25 of NDMA, NDEA, and NMOR which is 0.0217, since there was no significant difference (section 4.4.5.1).

Table 6 Calculation of SED, MoE and LCR in children of different ages based on a daily exposure of 12.5 ng and 100% absorption (BfR approach).

Age	Weight (kg bw)	SED (ng/kg bw/day)	MoE*	LCR (10^{-5})
6–12 months	9	1.39	13,000	0.11
1–2 years	12	1.04	17,000	0.17
2–4 years	15	0.83	21,000	0.08
4–10 years	30	0.42	42,000	0.12
10–16 years	55	0.23	78,000	0.07
0.5-16 years	NA	NA	NA	**0.55**

Note: *MoE rounded to the lower value with two significant figures.

The numbers of the RIVM approach are lower by a factor of about 4 (see annex IV).

4.4.5.3. Calculations of nitrosamine contaminations in balloons associated with a MoE of 10,000

The SCCS is aware of the limitations of risk characterisation using a MoE based on intermittent exposure during early life. This should be considered as a conservative approach. As another conservative assumption, instead of using individual BMDL10 values of nitrosamines found in balloons, the most potent and best investigated nitrosamine, NDEA, was used for the calculation of the MoE.

Associated with a MoE of 10,000 or higher from exposure to NDEA, and based on the BMDL10 of 18 µg/kg bw/d (see table 1), it follows that a lifetime exposure with nitrosamines of a child (6 months to 16 years old, 9-55 kg body weight) from sucking/chewing 10 cm^2 balloon material should not exceed 1.8 ng/kg bw/d, or a total of 16.2-99 ng/day. This corresponds to a maximum contamination (as determined by migration into artificial saliva) of 64.8-396 µg, respectively total nitrosamines/kg rubber. (balloon material)

The SCCS emphasises that these levels merely provide information on product specific contamination levels connected to a MoE of 10,000, and they do not provide distinction between safe from non-safe contamination levels.

Based on the LCR calculation, it was found that a level of nitrosamines of 50 µg/kg resulted in an exposure of 12.5 ng/d and a LCR of $0.55*10^{-5}$ for the age group 6 months-16 years, it follows that a level of nitrosamines of about 100 µg/kg will give a LCR for the age groups involved of about 10^{-5}.

5. CONCLUSIONS AND RECOMMENDATIONS

Additional Lifetime Cancer Risk

The SCCS concludes that the decision between the risk levels "serious" and "less than serious" is in the end a risk management decision. However, the SCCS considers that an additional LCR of 1×10^{-5} or a MoE of 10,000 based on a BMDL10, or a MoE of 25,000 based on T25 may be suitable as a practical approach to differentiate between the risk levels. It should be noted that this refers to life time exposure and not intermittent exposure.

Risk calculation for NDELA in cosmetics and nitrosamines in balloons

On the basis of the different approaches mentioned in the terms of reference, a reliable VSD for NDELA in cosmetics and nitrosamines in balloons cannot be calculated. The SCCS has used state-of-the-art methods to calculate LCR and MoE (see tables 2 and 6).

Safety assessment for children

The SCCS is of the opinion that based on the variations between different carcinogenicity studies and the uncertainty in relation to low dose extrapolation the use of Age Dependent Adjustment Factors represents a marginal effect and therefore there is no need to use additional uncertainty factors, except for calculations when the exposure occurs only during childhood and no data are available indicating that children have the same sensitivity in relation to cancer risk.

Nitrosamine contaminations associated with a MoE of 10,000 and a LCR less than 10^{-5}

As a pragmatic approach, the concentration of NDELA in cosmetics and nitrosamines in balloons has been back-calculated from the starting point of a MoE of 10,000 based on a BMDL10 and a LCR of 10^{-5} based on T25 values.

The SCCS emphasises that these levels merely provide information on product specific contamination levels connected to a MoE of 10,000, and they do not provide distinction between safe and non-safe contamination levels. Moreover, the calculations refer to a life time exposure and do not reflect intermittent exposure, which provides further conservatism.

6. ABBREVIATIONS

ADAF(s)	Age Dependent Adjustment Factor(s)
BfR	Bundesinstitut für Risikobewertung
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower (one-sided) 95% confidence bound
BMDL10	BMDL calculated for the BMR = 10%
BMR	Benchmark Response level

CPDB	Carcinogenic Potency Database
ECDC	European Centre for Disease prevention and Control
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
G6PDH	Glucose-6-phosphate dehydrogenase
GPSD	General Product Safety Directive
HT25	Represents the human equivalent dose of T25
LCR	(additional) Lifetime Cancer Risk
LED10	The 95% lower confidence limit on a dose associated with 10% extra tumour risk adjusted for background, equivalent to a BMDL10
LMS	Linear Multistage Model
MoE	Margin of Exposure
MS	Member State
SED	Systemic Exposure Dose
NBHPA	N-nitrosobis(2-hydroxypropyl)amine
NDBA	N-nitrosodibutylamine
NDEA	N-nitrosodiethylamine
NDELA	N-nitrosodiethanolamine
NDMA	N-nitrosodimethylamine
NHMOR	N-nitroso-2-hydroxymorpholine
NMEA	N-nitrosoethylamine
NMOR	N-nitrosomorpholine
NPYR	N-nitrosopyrrolidine
PoD	Point of Departure
RAPEX	Rapid alert system for non-food consumer products
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
RIVM	Rijksinstituut voor Volksgezonheid en Milieu
RP	Reference Point
RSD	Risk Specific Dose
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SF	Slope Factor
T25	The dose giving a 25% increase in the frequency of a specific tumour during the standard lifetime of the species studied.
TD50	The daily dose rate required to halve the probability of remaining tumorless at the end of a standard life-span
USEPA	United States Environmental Protection Agency
VSD	Virtually Safe Dose
WHO	World Health Organization

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ANNEX I

Annex I reviews all carcinogenicity studies on animals considered for the risk assessment of the nitrosamines considered in this opinion.

The available dose-response information is summarised for each study and it is indicated when a study was eligible for the calculation of a BMDL10 used for the MoE approach. The calculation of the BMD/BMDL was performed using BMDS software versions 2.2 of USEPA and PROAST software of RIVM (NL).

I.1 Studies used for N-nitrosodiethanolamine NDELA (CAS No. 1116-54-7)

Dose-response information on NDELA was available from six studies: Berger et al. (1987), Berger et al. (1990), Hecht et al. (1989), Lijinsky et al. (1984b), Lijinsky and Kovatch (1985), Preussman et al. (1982) and Zerban et al. (1988), which are briefly summarised below.

Preussmann et al (1982) administered NDELA p.o. through drinking water via 5 ml of an aqueous solution of NDELA per rat to a total of n = 340 Sprague Dawley rats (approximately 100 days old, 2-4 animals per cage) at the necessary concentration to obtain a daily dose of 1.5, 6, 25, 100 and 400 mg/kg body weight per day for 88, 72, 72, 36, 36 and 36 animals, respectively. Treatment was repeated 5 times/week; at the weekend tap water was given for 2 days ad libitum. Untreated controls received tap water only. All animals were allowed to die naturally or were killed when moribund. NDELA treatment at the five dose levels resulted in a significant number of animals with benign and malignant liver tumours (predominantly hepatocellular carcinomas and adenomas but also mesenchymal hemangioendotheliomas, cholangiofibromas and cholangiocarcinomas). Neoplasms in the nasal cavity (comprising squamous cell carcinomas and neuroepitheliomas) were also observed. Liver tumours occurred with median latencies of 938, 840, 632, 465, 357 days in the five dose groups at the frequencies of 7/72, 43/72, 33/36, 32/36 and 31/36, respectively; none (0/88) in the control group. Tumours at organ sites other than the liver were considered as not treatment related.

The liver tumour data were suitable for the BMD approach. Tumour incidence was saturated at or near 100% in the three highest doses the BMD and no model fitted the data acceptably when all five or the four lowest dose groups were included in the analysis. Therefore the BMD analysis was performed without the two highest doses and a BMDL10 value of 0.55 mg/kg bw/day was derived when selecting the Weibull model with a BMDL10 of 0.95 mg/kg bw/day.

Lijinsky et al. (1984b) compared five different hydroxylated nitrosodialkylamines. NDELA was supplied in drinking water to a group of 16 female F344 rats (7-8 weeks old) for 50 weeks at one single (total) dose of 2,000 mg (15 mmol) given 5 days per week at the rate of 80 ml per cage. According to the publication, after 90 weeks all animals died naturally after end of treatment or were killed when moribund with liver carcinomas in 15 animals, with 13 animals with tumours in nasal cavity and with five other tumours. None of these tumours were observed in the controls (20 untreated animals). No body weight data were reported and no BMD analysis was performed since the design used only a single dose.

Lijinsky and Kovatch (1985) administered NDELA in drinking water to a total of 126 F344 rats (7-8 weeks old) of both sexes in a balanced design at dose levels of 0 and 28 mg/L for 100 weeks, 64 mg/L for 100 and 50 weeks, and 160 mg/L for 50 weeks in drinking water, observed at maximum 130 weeks. Average daily doses were calculated to 280, 320, 640 and 800 mg per rat in the four dose groups, respectively. The number of

animals per sex and treatment group varied from 20 to 39. Compared with the controls (20 males, 20 females), a statistically significant increase in the incidence of hepatocellular carcinoma was observed in females at 64 mg/L treated for 100 weeks and in males and females at 160 mg/L treated for 50 weeks. The number of neoploastic liver nodules was increased in all dose groups and a few cholangiocellular carcinomas and adenomas were reported. In the four dose groups together ten animals with kidney tumours and five with stomach papillomas were observed. A combined dose-response analysis could be performed when using average total dose of 280, 640 320, 800 mg in the four dose groups, respectively. No BMD analysis was performed since only two dose groups could be analysed for each of the two treatment durations and no body weight data were available.

Zerban et al. (1988) studied the number and extent of enzyme altered liver foci (preneoplastic lesions) in a dose-time experiment when administering NDELA to male Sprague Dawley rats (weighing approx. 280 g when purchased) in drinking water. The rats (two per cage) were randomised into a control (n = 50) and five dose groups with doses of 0.2, 0.63, 1.5, 6 and 25 mg/kg bw/day for 5 days/week The experiment used n = 54 animals in each dose group for a maximum of 24 months with interim sacrifices at 12, 15, 18, 21 months of 10 animals each time. The primary endpoint was the number and size of glucose-6-phosphate dehydrogenase (G6PDH) positive foci. There was a clear dose-time response of the area density of G3PDH positive foci.

Hepatocellular carcinomas were primarily seen at the highest dose level (1/10 after 15, 9/10 after 18 and 10/10 after 21 months, respectively. Only three hepatocellular carcinomas were seen at lower doses. Dose-dependent incidence of hepatocellular carcinomas was analysed after 2 years where the total number of carcinomas among animals examined after 24 months was 0, 0, 0, 0, and 3.6 in 6, 9, 14, 9, 9, and 6, animals surviving by that time in the control and the five dose groups, respectively. There was a dose-response effect also at earlier times: at 21 months with incidences (0, 0, 1, 0, and 1) and at 18 months with (0, 0, 0, 0, 0, and 9) each per 10 animals. A BMD analysis was not performed due to the dose-time design and mortality differences in the dose groups over the 24 months duration, and was therefore not performed.

Hecht et al. (1989) investigated NDELA, NMOR and NHMOR in one study. A group of 40 A/J female mice was treated with a total 55 µmol NDELA for 10 weeks (0.2 µmol/ml drinking water) and compared with a control group (n = 40) after 30 weeks for lung tumour incidence. The investigators observed 70% incidence in the NDELA group versus 40% in the control group. The mean number of lung tumours per mouse was increased in the NDELA group.

A total of 20 female F344 rats were treated for 50 weeks (observed for a maximum of 120-124 weeks) at a total dose of 150 mg/L in drinking water for 50 weeks. Compared to a control group (n = 20) without tumours, 14/20 animals given NDELA exhibited hepatocellular carcinomas. No BMD analysis was performed since the design used only one dose and body weight data were not reported.

Berger et al. (1987) and Berger et al. (1990) reported a dose-response analysis in a total of n =1,800 male Sprague Dawley rats (mean age 100 +/- 10 days) designed to assess syncarcinogenicity of NDEA, NPYR and NDELA in the liver when administered lifelong in drinking water. After 4 months the diet was restricted to 21 g per animal to maintain a mean body weight of 420 g. NDELA was given at 2.0, 0.63 and 0.2 mg/kg bw/day to 80 animals in each group and compared with a control group of 500 animals. Incidence of liver tumours in the controls and the three dose groups was 3/500, 2/80, 1/80 and 6/80, respectively. Among the nine animals with liver tumours in the three dose groups were four with hepatocellular carcinomas and one with an adenoma, three

with benign hemangioendothelioma and one with a cholangioma. Other tumours were without well-defined dose-response dependency. Median survival was not statistically significantly reduced in all three NDELA dose groups. The percentage of malignant tumour bearing animals was 29% in the control group and 35-36% in the three NDELA groups.

These data were suitable for the BMD approach and a BMD10 = 3.37 and a BMDL10 = 1.74 mg/kg bw/day was derived based on the Weibull model.

SCCS noted that the BMDL10 (1.74 mg/kg bw/day) derived from Berger et al. (1987) is a factor of more than 3 higher than the BMDL10 of 0.55 mg/kg bw/day derived from the data of Preussmann et al. (1982). The design and precision of the two studies are comparable (performed in the same institute about 5 years apart and of the same high quality using the same pathologist). Combining the data of both studies, a joint BMDL10 of 0.73 mg/kg/d was calculated. A covariate analysis, using the PROAST software (version 32.2), of the two studies revealed a BMDL10 of 0.56 mg/kg/d which is quite close to 0.73 mg/kg/d.

I.2 Studies used for N-nitrosodimethylamine NDMA (CAS No. 62-75-9)

The SCCS identified five studies from which dose-response information on NDMA in animals was available: Arai et al. (1979), Lijinsky and Reuber (1984a), Lijinsky et al. (1987), Peto et al. (1991b) and Terao et al. (1978).

Terao et al. (1978) administered, when investigating synergistic effects with sterigmatocystin, 10 ppm NDMA given in the diet to n = 15 (4 weeks old) male Wistar rats for 54 weeks and compared the results with tumour incidence in n = 30 animals in the control group (killing one in each group after 5 weeks of feeding). No hepatic carcinomas were found after 69 weeks in both groups, but 7/15 Leydig cell tumours were seen in the NDMA group. Summaries of body weight and water and food consumption data are reported. No BMD analysis was performed since the design used only one dose.

Arai et al. (1979) treated 24 male and 24 female Wistar rats with NDMA at concentrations of 0.1, 1 and 10 ppm in the diet for 96 weeks using a control group of 18 males and 18 females. All animals were 6 weeks old with males starting with 120 g and females with 101 g average weight. From the originally 140 animals in control and treatment groups, only103 were available for liver assessment. Liver tumour incidence was reported after complete necropsy after 96 weeks for 19, 26, 32 and 26 animals in the control and the three respective dose groups separating between liver cancer (0/19, 0/26, 4/32 and 3/26), hemangioendotheliomas (0/19, 0/26, 1/32 and 6/26) and fibrosarcomas (0/19, 0/26, 1/32 and 5/26) in the control and the respective three dose groups. No joint incidence of liver tumours could be determined. Tumours were also reported for pituitary gland (n = 3), testis (24), ovary (1) and other sites (7). Since a large portion of animals was not examined these data were not subject to a BMD analysis.

Lijinsky and Reuber (1984a) investigated four nitroso-methylalkylamines in groups of 20 F344 female rats (7-8 weeks old, four rats housed per cage). NDMA was administered in drinking water at doses of 5.5 and 13 mg/L, respectively, for 30 weeks, 5 days per week. The rats were observed for a maximum of 110 weeks. A total of 14/20 and 17/20 animals with liver tumours were reported (carcinomas 9/20 and 10/20, hemangiosarcomas 0/20 and 7/20, and neoplastic nodules 2/20 and 4/20) in the two

dose groups and compared to 4/20 in the control group. No BMD analysis was performed since only two dose groups and no body weight data were available.

Lijinsky et al. (1987) treated in a study of three nitroso-dialkylamines (NDMA, NDEA, NMEA) and Azoxyalkane n = 20 male F344 rats (8 weeks old) with NDMA at a concentration of 10 mg/mL (dosing 0.2 m × 2/week for 30 weeks corresponding to 4 mg/week and a total dose of 120 mg) and n = 50 male Syrian Gold hamsters (in three groups of 20, 20, and 10) with 7.5 mg/mL NDMA (dosing 0.2 mL × 1/week, 0.1 mL × 2/week and 0.1 mL × 1 /week, respectively), for 4, 6.5 and 20 weeks. This resulted in total doses of 6, 10, and 15 mg per animal, respectively. Liver carcinoma incidence was 50% (10/20) in rats and 11/20, 3/20, 6/10 in hamster, respectively. In rats, kidney (10/20), nasal (3/20) and lung (16/20) tumours coincided. In the high dose group of hamsters the median time to death with tumour was only 29 weeks compared to 44 and 41 weeks in the two low dose groups of 6 and 10 mg total dose. No control group and no body weight data of the animals were reported, and no BMD analysis was performed.

Peto et al. (1991b) examined, in a large dose-response study, 1,120 male and 1,120 female inbred Colworth rats at 15 concentrations of NDMA present in the drinking water starting at about 6 weeks of age and continuing throughout life. NDMA was administered in the lowest dose group at a concentration of 0.033 ppm (group 2) and increased by doubling that dose in six steps (group numbers 3-7) to 1.056 ppm. The next highest groups (group numbers 8-15) were obtained by increasing the dose stepwise by a factor ranging between 1.5 and 1.2, such that dose group number 15 received NDMA at 8.448 ppm. The highest dose was given to group number 16 (16.896 ppm). Each dose group had, in general, n = 60 animals and the control (group number 1) had n = 240. There was a clear sigmoidal dose-response relationship in the incidence of fatal liver tumours (liver cell, bile duct, mesenchyme, Kupffer cell neoplasms) with incidences of 1, 1, 3, 3, 3, 3, 13 in males and of 1, 1, 0, 2, 3, 5, 5 in females in the control and the lowest 6 dose groups, respectively. Prevalence of incidental tumours showed no dose-response relationship. A BMD analysis was performed separately for males and females using the six lowest dose groups (maximum of 1.056 ppm) and the control group. The BMDL10 was calculated for males and females (0.64 and 0.56 ppm concentration of NDMA in drinking water) and transformed into an equivalent intake of 0.027 and 0.041 mg/kg bw/day, respectively.

I.3 Studies used for N-nitrosodiethylamine NDEA (7261-97-4)

NDEA

The SCCS identified seven studies from which dose-response information on NDEA in animals was available: Berger et al. (1987), Berger et al. (1990), Druckrey et al. (1967), Habs and Schmähl (1980), Lijinsky et al. (1981), Lijinsky et al. (1983), Lijinsky et al. (1987) and Peto et al. (1991b).

Habs and Schmähl (1980) report, from a study on synergistic effects of n-nitroso compounds, an incidence of liver tumours of 45% (36/80) for Sprague Dawley rats treated with 0.1 mg/kg bw/d, 5 days per week, compared with a control group where no tumours were seen in 82 rats (the number of rats were adjusted for deaths from other causes) at a median induction time of 760 days. Esophageal tumors were observed in 33/80 treated animals. No BMD analysis was performed since the design used only one dose and no body weight data were reported.

Lijinsky et al. (1981) studied NDEA in F334 female rats (6-8 weeks old) in 10 dose groups and a control group each with n = 20 (except one group of 12) animals and with time to death as the primary endpoint. The NDEA concentrations in drinking water varied from 113 down to 0.45 mg/L. The solutions of 113 and 45 mg/L were administered for 17 and 22 weeks (two groups). The 18, 7, 2.8, 1.1, and 0.45 mg/L solutions were all given for 30 weeks (five groups). In addition 1.1 mg/L was given to another group of rats for 60 weeks, and 0.45 mg/L was given to an additional group for 60 and 104 weeks. Liver tumour incidence was reported for all groups distinguishing five subtypes. The total dose was calculated to be 1.4, 2.7, 3.3, 4.7, 6.6, 8.4, 21, 54, 99, and 192 mg for the 10 dose groups. Incidence of hepatocellcarcinomas in the 10 dose groups were 1, 6, 5, 4, 3, 5, 1, 1, 9, 17 compared to none in the control group. A total of 28 sites were investigated for tumour incidences varying between 0% and almost 100% tumour incidence. In the absence of body weight data and given the complex dose-time design, no BMD analysis was performed.

Lijinsky et al. (1983) studied five nitroso compounds. NDEA was administered to female F344 rats (7-8 weeks old) at 7 mg/L in drinking water 5 days/week for 30 weeks in four groups of 20 animals each in combination with groups of animals treated with another nitroso compound. Highest incidence was observed for oesophagus tumours (16.1, 8, 14 and 17/20) compared to no tumours in the control group. Incidence of liver tumours was low. No BMD analysis was possible since the design used only a single dose. No body weight data were reported.

Lijinsky et al. (1987) treated, in a study of three nitroso-dialkylamines (NDMA, NDEA, NMEA) and Azoxyalkane, 20 male F344 rats (8 weeks old) with NDEA at the concentration of 12.5 mg/mL for 20 weeks corresponding to 5 mg/week and a total dose of 100 mg and 30 male Syrian Gold hamsters (in groups of 20 and 10) with 10 mg/mL NDMA for 25 and 20 weeks corresponding to a total dose of 50 and 20 mg per animal. Liver carcinoma incidence was 16/20 in rats and 17/20 and 3/20 in hamster, respectively. No weight data were reported. In rats, oesophagus (11/20) and nasal (14/20) tumours coincided. In the high dose group of the hamsters the median time to death with tumour was 47 weeks, which was lower than in the low dose group where the time was 69 weeks. No control group was reported and no BMD analysis was performed.

Berger et al. (1987) and Berger et al. (1990) reported a dose-response analysis in a total of n = 1,800 male Sprague Dawley rats (mean age 100 +/- 10 days) designed to assess syncarcinogenicity of NDEA, NPYR and NDELA in the liver administered lifelong in drinking water. After 4 months diet was restricted to 21g per animal to maintain a mean body weight of 420 g. NDEA was given at 0.01, 0.032 and 0.1 mg/kg bw/d to 80 animals in each group and compared with a control of 500 animals. Incidence of liver tumours in the controls and the three dose groups was 3/500 2/80 3/80 36/80. Among the 41 animals with liver tumours in the three dose groups, were 22 with hepatocellular carcinomas, five with an adenomas and 17 with malignant hemangioendothelioma. Other tumour types were without well defined dose-response dependency. Median survival was statistically significantly reduced in the two highest dose groups. The percentage of malignant tumour bearing animals was 29% in the control group and 29-65% in the three NDEA groups.

The SCCS derived from these data BMD10 = 0.043 and a BMDL10 = 0.033 mg/kg bw/d was based on the Multistage Cancer model.

Peto et al. (1991b) examined, in a large dose-response study, 1,120 male and 1,120 female inbred Colworth rats at 15 concentrations of NDEA in the drinking water starting at about 6 weeks of age and continuing throughout life. NDEA was administered at the

lowest dose at a concentration of 0.033 ppm (group 2) and increased by doubling that dose in six steps (group numbers 3-7) to 1.056 ppm. The groups with numbers 8-15 were obtained by increasing the dose stepwise by a factor ranging between 1.5 and 1.2, such that group 15 received NDEA at 8.448 ppm. The highest dose was given to group 16 (16.896 ppm). The dose groups had in general n = 60 animals and the control (group 1) n = 240. There was a clear sigmoidal dose-response relationship in the incidence of fatal liver tumours (liver cell, bile duct, mesenchyme, Kupffer cell neoplasms) with incidences of 1, 1, 0, 5, 2, 4, and 8 in males and of 1, 0, 0, 1, 1, 3, and 23 in females in the control and the six lowest dose groups, respectively. Prevalence of incidental tumours showed no dose-response relationship .A BMD analysis was performed separately for males and females using the control and the six lowest dose groups (maximum of 1.056 ppm). The BMDL10 was calculated for males and females to the value of 0.42 ppm concentration of NDMA in drinking water for both) and transformed into an equivalent intake of 0.018 and 0.030 mg/kg bw/d, respectively.

Druckrey et al. (1963) and Druckrey et al. (1967) reported for the first time on liver tumours in 255 out of a total of 274 surviving BD II rats dosed at 0.075 to 14 mg/kg bw/d in drinking water 7 days per week. Median time to death with liver tumour ranged between 840 and only 68 days depending on total dose ranging between 64 to 1,000 mg/kg bw/d. The study aimed at determining the tumour induction time depending on the total dose. Therefore, the median induction time was determined in groups of 7, 30, 67, 49, 36, 34, 25, 25, 5 animals dosed at 0.075, 0.15, 0.3, 0.6, 1.2, 2.4, 4.8, 9,6, 14 mg/kg bw/d, respectively (with 5, 27, 67,49, 36, 34, 25, 25, 5 tumour bearing animals). Since these data report only the number of tumour bearing animals and not the number of animals at start of the experiment no dose-response analysis is possible and no BMD analysis was performed.

Additional studies were performed by this group on guinea pigs (Druckrey and Steinhoff, 1962) and on hamster, mice, rabbits, monkey, dogs, and fish by others at that time as reported by Druckrey et al. (1967). Furthermore, NDEA was also administered i.v. in 36 rats at 2.1 mg/kg bw once per week with liver tumours seen in 26 animals, corresponding the incidence of 0.3 mg/kg bw/d given orally.

I.4 Studies used for N-nitrosodibutylamine NDBA (924-16-3)

The SCCS identified two studies on N-nitrosodibutylamine (NDBA) (see also USEPA IRIS: http://www.epa.gov/iris/subst/0037.htm).

Druckrey et al. (1967) treated a total of 40 BD rats with N-nitrosodibutylamine in dietary concentrations at 10, 20, 37.5, or 75 mg/kg bw/day lifelong. No control data were reported. All four surviving animals of the high dose group developed liver tumours as well as 13/16, 4/10, and 2/10 in the 37, 20, and 10 mg/kg bw/day groups. There were animals with multiple tumours in all dose groups. In addition to liver tumours, oesophageal tumours (5/16) and bladder tumours (5/16) were observed at the second highest dose of 37.5 mg/kg bw/d as well as in the next lower dose group of 20 mg/kg bw/d (oesophagus: 8/10, bladder: 7/1). There were 2-3 animals with liver tumours in the lowest dose group (one carcinoma and two adenomas) but also tumours of the pharynx (3), oesophagus (one carcinoma and one adenoma), and bladder (two carcinoma and four adenoma bearing animals). The SCCS derived from these data a BMD10 of 2.9 and BMDL10 value of 2.0 mg/kg bw/d based on the quantal linear: 2.9/2.0 (p=0.56); loglogist: 15.0/3.7 (p=0.7); logprobit: 15.5/4.0 (p=0.8); Gammamodel.

Druckrey et al. (1967) also reported a study where N-nitrosodibutylamine was administered s.c. to 20 BD rats once per week at 220 and 400 mg/kg bw resulting in squamous cell carcinoma in bladder in 18/20; liver tumours in 2/20 had and oesophageal tumours in 3/20 animals.

Bertram and Craig (1970) exposed 50 male and 50 female C57BL/6 mice (10 per cage, 10-12 weeks old) to either 30 mg/kg bw/d or 7.6 mg/kg bw/d NDBA (mean dosage) in drinking water. In the high dose group, exposure of half of the animals was stopped after 197 days when gross haematurea was observed. Squamous-cell carcinomas of the bladder were seen in 44/90 (36 males and eight females) for the high-dose group of these mice. There was no difference regardless of whether treatment was ceased or not. In the low dose group 19/89 mice developed bladder tumours (17 males and two females). Since there were only two dose groups and no control in this study, no BMD analysis was performed.

I 5 Studies used for n-nitrosomorpoline NMOR (59-89-2)

The SCCS identified three studies from which dose-response information on NMOR in animals was available: Hecht et al. (1989), Lijinsky and Reuber (1982) and Lijinsky et al. (1988).

Lijinsky and Reuber (1982) investigated three nitroso compounds and treated three groups of n = 20 F344 rats (four per cage) 5 days per week for 50 weeks with NMOR at two concentrations: 20 male rats at 16 mg/L, 20 male rats at 40 mg/L, and 20 female rats at 40 mg/L in drinking water. Over a maximum period of 110 weeks, liver carcinoma occurred in 18/20 male rats at the low dose and in 19/20 male and 17/20 female rats at the high dose. Liver sarcoma were observed at the high dose in 15/20 males and 17/20 females and in the low dose group in 4/29 males. Oesophagus carcinoma were observed at the high dose in 3/20 females. Having only two dose groups, no control and no body weight data, a BMD analysis was prohibited.

Lijinsky et al (1988) reported the results of a large carcinogenicity study on female F344 rats (four per cage, 8 weeks old) treated for 25, 40, 50 and 100 weeks at various doses of NMOR. Maximum observation lasted for 126 weeks.

Treatment with 100 mg/L for 25 weeks and 20 mg/L for 40 weeks resulted in 15/24 and 16/24 hepatocellular carcinomas and an even higher incidence of hemangiosarcomas (24/24 and 23/24).

In the substudy of 50 weeks treatment the control group of 80 rats showed no hepatocellularcarcinomas or hemangiosarcomas. The incidence of hepatocellular carcinomas was 0/48, 1/48, 5/48. 7/24 and 15/23 at doses 0.45, 1.1, 2.6, 6.4 and 16.0 mg/L, respectively, with a highly statistically significant trend. For hemangiosarcomas the incidence was lower with 0/48, 0/48, 1/48, 0/24 and 8/23.

In the substudy of 100 weeks treatment the (same) 80 rats in the control group still showed no hepatocellularcarcinomas or hemangiosarcomas. The incidence of hepatocellular carcinomas was 1/100, 0/99, 0/47, 1/48, 7/48, and 16/24 at the doses of 0.07, 0.18, 0.45, 1.1, 2.6 and 6.4 mg/L, respectively, again with a highly statistically significant trend. For hemangiosarcomas the incidence was lower with 0/100, 0/99, 0/47, 0/48, 5/48, and 13/24, but showed also a highly statistically significant trend.

The SCCS derived from these data a BMDL10 value of 1.7 mg/L with a BMD ranging between 2.3 and 7 mg/L for the Weibull, Multistage, Gamma, loglogist and logprobit models. Using the conversion indicated in the publication of BMDL10 of 0.7 mg/kg bw/d was derived for the 100 week study. The 50 week study gave a BMDL10 value of 1.5 mg/L (quantal linear model) with a BMDL10 of 2.1 mg/mL converted to BMDL10 of 0.65 mg/kg bw/d. From these results a BMDL10 = 0.7 was established as a reference point for hepatocellular carcinoma incidence.

Hecht et al. (1989) investigated NDELA, NMOR and NHMOR. A group of 40 A/J female mice was treated with 54 µmol NMOR for 10 weeks (0.2 µmol/ml drinking water) and compared with a control group (n = 40) after 30 weeks for lung tumour incidence. Under treatment with NMOR 100% incidence and a mean of 20 tumours per lung was observed compared to 40% in the control group. A total of 20 female F344 rats were treated for 50 weeks (observed at maximum 80 weeks) at total dose of 0.6 mmol (26.5 mg/L) in drinking water. Compared with a control group (n = 20) with no tumours, the group given NMOR exhibited hepatocellular tumours in 19/20 rats; 10/20 rats exhibited hemangiosarcomas. In the absence of body weight data and only one dose group available no BMD analysis was performed.

Annex II

N-nitrosodiethanolamine NDELA (CAS No. 1116-54-7)

Table II.1 Calculation of T25 and HT25 from carcinogenicity studies of NDELA on rats[1].

T25: HT25 (mg/kg bw/day)	Target	Species	Route	Exposure (week)	Obser-vation (week)	Lowest tumour frequency (%)	Ref(s)
2.19: 0.64	Liver	F344 rats male	Drinking water	100	104	20	Lijinsky and Kovatch (1985)
1.79: 0.47	Liver	F344 rats female	Drinking water	100	104	35	Lijinsky and Kovatch (1985)
2.22: 0.65	Liver	SD rats male	Drinking water	116	116	60	Preussman et al. (1982)
8.09: 2.28	Liver	SD rats male	Drinking water	130	130	1.9	Berger et al. (1990)
3.21: 0.94	Liver	SD rats male	Drinking water	104	104	33	Zerban et al. (1988)
1.05: 0.28	Liver[2]	SD rats female	Drinking water	50	104	70	Hecht et al. (1989)

Notes: [1] The T25 is calculated from the experimental data as described by Dybing et al (1997). HT25 values represent the human-equivalent dose estimated from the rat studies by using a scaling factor based on body weight to the power of ¾ as described by Sanner et al. (2001). Unless the specific weights are given, the following defaults are used (humans = 70 kg, male rats 500 g and female rats 350 g (ECHA 2008). Studies with exposure time less than 50 weeks and studies where the frequency of hepatocellular tumours at the lowest dose tested were 80% or higher were excluded.

[2] Type of hepatocellular tumours not specified.

The experiment by Berger et al. (1990) has been excluded from the calculation of the mean as it is more than seven times standard division above the mean.

Mean T25 = 2.09 ± 0.78 mg/kg bw/d (range 1.05–3.21 mg/kg bw/d)

Mean HT25 = 0.60 ± 0.24 mg/kg bw/d (range 0.28–0.94 mg/kg bw/d)

N-nitrosodibutylamine NDBA (CAS No. 924-16-3)

Table II.2 Calculation of T25 and HT25 from carcinogenicity studies of NDBA on rats.

T25: HT25 (mg/kg bw/day)	Target	Species	Route	Exposure (week)	Obser-vation (week)	Lowest tumour frequency (%)	Ref(s)
0.37: 0.11	Liver carcinoma	F344 rats male	Gavage	30	104	60	Lijinsky and Reuber (1983)

T25 = 0.37 mg/kg bw/d

Mean HT25 = 0.11 mg/kg bw/d

TD50 = 0.691

N-nitrosodimethylamine NDMA (CAS No. 62-75-9)

Table II.3: Calculation of T25 and HT25 from carcinogenicity studies of NDMA on rats.

T25: HT25 (mg/kg bw/day)	Target	Species	Route	Exposure (week)	Obser-vation (week)	Lowest tumour frequency (%)	Ref(s)
0.11: 0.032	Lung scc	F344 rats male	Gavage	30	45	32	Lijinsky et al. (1987)
0.041: 0.012	Liver carcinomas	F344 rats male	Drinking water	30	80	50	Lijinsky and Reuber (1984a)
0.032: 0.0085	Liver carcinomas	F344 rats female	Drinking water	30	90	45	Lijinsky and Reuber (1984a)
0.73: 0.22	Leydig cell	Wistar rats male	Feed	54	69	47	Terao et al. (1978)
0.059: 0.017	Liver malignant	Wistar rats male	Drinking water	104	104	22	Peto et al. (1991a)
0.044: 0.012	Liver malignant	Wistar rats female	Drinking water	104	104	45	Peto et al. (1991a)
0.061: 0.016	Liver carcinomas	Wistar rats female	Feed	93	93	18	Arai et al. (1979)

The results of Terao et al. (1978) were not included in the risk assessment because the study is based on Leydig cell tumours).

Peto 1991 (cited):

"The linear relationship observed at low dose rates (below 1 ppm) suggests that under these experimental conditions, among rats allowed to live their natural life span, a dose of 1 ppm of NDEA or NDMA in the drinking water will cause about 25% to develop a liver neoplasm."

Male rat, 25 ml per day, 500 mg; 1 ppm represent 0.001 mg/ml, 0.025 mg/0.500 = 0.050 mg/kg bw/d; female rat 20 ml per day, 350 g; 0.001 mg/ml, 0.020 mg/0.350 = 0.057 mg/kg bw/d. The above citation implies a T25 of 0.050–0.057 mg/kg bw/d both for NDMA and NDEA.

Mean T25 = 0.058 ± 0.028 mg/kg bw/d (range 0.032–0.11 mg/kg bw/d)

Mean HT25 = 0.016 ± 0.008 mg/kg bw/d (range 0.0085–0.032 mg/kg bw/d)

TD50 = 0.096 (rat, there is more than one positive experiment, variation is greater than 10-fold among statistically significant (two-tailed $p<0.1$) TD50 values from different positive experiments).

N-nitrosomorpholine NMOR (CAS No. 59-89-2)

Table II.4: Calculation of T25 and HT25 from carcinogenicity studies of NMOR on rats.

T25: HT25 (mg/kg bw/day)	Target	Species	Route	Exposure (week)	Obser-vation (week)	Lowest tumour frequency (%)	Ref(s)
0.123: 0.033	Liver carcinomas	F344 rats female	Drinking water	50	100	10	Lijinsky et al. (1988)
0.047: 0.014	Liver carcinomas	F344 rats male	Drinking water	50	80	90	Lijinsky and Reuber (1982)
0.122: 0.032	Liver carcinomas	F344 rats female	Drinking water	50	55	85	Lijinsky and Reuber (1982)
0.082: 0.022	Liver carcinomas	F344 rats female	Drinking water	50	65	95	Hecht et al. (1989)

Mean T25 = 0.094 ± 0.036 mg/kg bw/d (range 0.047–0.123 mg/kg bw/d)

Mean HT25 = 0.025 ± 0.009 mg/kg bw/d (range 0.014–0.033 mg/kg bw/d)

TD50 = 0.109 (rat, there is more than one positive experiment)

N-nitrosodiethylamine NDEA (CAS No. 55-18-5)

Table II.5: Calculation of T25 and HT25 from carcinogenicity studies of NDEA on rats.

T25: HT25 (mg/kg bw/day)	Target	Species	Route	Exposure (week)	Obser-vation (week)	Lowest tumour frequency (%)	Ref(s)
0.11: 0.032	Liver carcinomas	F344 rats male	Gavage	30	45	32	Lijinsky et al. (1987)
0.11: 0.031	Liver malignant	Wistar rats male	Drinking water	104	104	8	Peto et al. (1991a)
0.042: 0.011	Liver malignant	Wistar rats female	Drinking water	104	104	32	Peto et al. (1991a)
0.0088: 0.0023	Liver carcinomas	F344 rats female	Drinking water	60	104	30	Lijinsky et al. (1981)
0.19: 0.054	Liver carcinomas	SD rats Male	Drinking water	122	122	26	Berger et al. (1987)
0.030: 0.0081	Oesophagus unspecified	F344 rats female	Drinking water	30	45	89	Lijinsky et al. (1983)
0.049: 0.014	Liver unspecified	SD rats male	Drinking water	116	116	45	Habs and Schmähl (1980)

Mean T25 = 0.085 ± 0.065 mg/kg bw/d (range 0.0088–0.19 mg/kg bw/d)

Mean HT25 = 0.024 ± 0.019 mg/kg bw/d (range 0.0023–0.054 mg/kg bw/d)

TD50 = 0. 0265 (rat, there is more than one positive experiment, variation is greater than 10-fold among statistically significant (two-tailed $p<0.1$) TD50 values from different positive experiments) (TD50 based on the same data as T25 gives TD50 = 0.161 mg/kg bw/d).

ANNEX III

Nitrosamines found in cosmetics are described below. Mainly NDELA and NBHPA have been found in cosmetics. The other nitrosamines in the list have been found only very rarely in cosmetics and/or raw materials. Recent analytical surveys: BLGL (2007-2010), CVUA Karlsruhe (2005), CVUA Karlsruhe (2006), CVUA Stuttgart (2005), CVUA Stuttgart (2006), CVUA Stuttgart (2007), CVUA Stuttgart (2008), Eisenbrand et al. (1991), RIVM (2008), RIVM (2009), Schothorst and Stephani (2001), Schothorst and Sommers (2005), covering the time period from 2000 to present also confirm that these two nitrosamines were exclusively found. Values before 2000 from Germany (Eisenbrand et al. 1991) are also included for time trend information.

Table AIII.1 Nitrosamine Contents in Cosmetics of the European Market (data before 2000 and data without itemisation not considered for exposure assessment).

Country	Reference(s)	Method	Type of cosmetic	Total/ positives	Content (µg/kg range)	Median
Germany	Eisenbrand et al. (1991)	GC-TEA	All samples	126/19		
			Shampoo	10 / 3	70-150	110
			Foam bath/Shower gel	8 / 4	7-90	48 70
			Body lotion	6 / 3	7-130	-
			Suntan lotion	9 / 2	7- 2 000	85
			Cream	7 / 3	30-275	[1)]
			Scrub/Washing emulsion	3 / 3	20-175	25
Germany	Bayerisches Landesamt für Gesundheit und Lebensmittel-sicherheit (BLGL) (2007-2010)		All samples (NDELA)	450/39		
			Skin cleaning preparations	106 / 10	38-520	93
			Skin care preparations (body cream/lotion)			
			Decorative cosmetics	97 / 3	34-63	48
			Hair treatment products			
			Tattoo colours	113 / 17	27-349	60
				99 / 8	57-312	139
				35 / 1	73	
Germany	CVUA Karlsruhe (2006)		Various cosmetics	32 / 6		
			1 Hair gel		10 000	
	CVUA Karlsruhe (2005)		5 Mascara		79-370	
			Hand soap		40	
Germany	CVUA Stuttgart (2008)		Various cosmetics	63 / 9		
			4 Mascara		36-238	
			5 not specified		> 10	
	CVUA Stuttgart (2007)		Various cosmetics	65 / 6	> 10	
			Handwashing paste		1 723	
			Mascara		301	
	CVUA Stuttgart (2006)		Various cosmetics not specified	45 /12	> 10	

Country	Reference(s)	Method	Type of cosmetic	Total/ positives	Content (µg/kg range)	Median
	CVUA Stuttgart (2005)		Various cosmetics Handwashing paste	14 / 7	 17-415	
Netherlands	Schothorst and Stephani (2001)	GC-TEA	1. Part All samples Shampoo Shower gel Hair gel 2. Part All samples Shampoo Shower gel Lotion	 48 / 4 - - - 25 / 7 - - -	 53-187 185-190 7555-7733 217-1313 42 3873 218-248	 117 - - 382 1 756 -
Netherlands	Schothorst and Somers (2005)	LC-MS-MS	All samples Shower gel Cream / foam soap Shampoo Srub Hand/cream soap Hair oil (n = 1)	140/35 - - - - - -	 32-992 24-2692 23-945 24-67 26-75 26	 41 260 55 45 - -
Netherlands	RIVM (2009)		Mascara Eyeliner	72 /14 33 / 6	58-20000 20-223	206 40
Netherlands	RIVM (2008)		All Samples Shampoo (Cream)Bath/Shower gel/Soap	668/60 279 / 24 (7 : <50µg/kg) 244 / 22 (17 : <50µg/kg)	 83-56750 <50-660	 175 <50

Notes: [1)]NDELA plus NBHPA.

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ANNEX IV

The calculations of SED are shown in table IV.1.

Table IV.1 Calculation of SED and MoE (related to the BMDL10 of NDEA) in children at different ages based on a daily exposure of 12.5 ng and 100% absorption (BfR approach).

Age	Weight (kg bw)	BfR approach (12.5 ng/d)		RIVM approach (0.64-3.25 ng/d)	
		SED (ng/kg bw/day)	MoE*	SED#	MoE*
6–12 months	9	1.39	13,000	0.07-0.36	50,000
1–2 years	12	1.04	17,000	0.05-0.27	67,000
2–4 years	15	0.83	21,000	0.04-0.22	82,000
4–10 years	30	0.42	42,000	0.02-0.11	160,000
10–16 years	55	0.23	78,000	0.01-0.06	300,000

Notes: *MoE rounded to the lower value with two significant figures.
MOE calculated only for the upper bound

NDMA HT25 = 0.016

NDEA HT25 = 0.024

NMOR HT25 = 0.025

Mean HT25 = 0.0217

Table IV.2 Calculation of LCR from the mean HT25 in children at different ages based on a daily exposure of 12.5 ng and 100% absorption (BfR approach) and for the age group 6 months to 16 years.

Age	Weight (kg bw)	BfR approach (12.5 ng/d)		RIVM approach (0.64-3.25 ng/d)	
		SED (ng/kg bw/day)	LCR (10^{-5})	SED	LCR (10^{-5})
6–12 months	9	1.39	0.11	0.07-0.36	0.03
1–2 years	12	1.04	0.17	0.05-0.27	0.04
2–4 years	15	0.83	0.08	0.04-0.22	0.02
4–10 years	30	0.42	0.12	0.02-0.11	0.03
10–16 years	55	0.23	0.07	0.01-0.06	0.02
6 months–16 years			**0.55**		**0.14**

The theoretical LCR was calculated on the basis of exposure to nitrosamines from balloons during the age of 6 months to 16 years.