Scientific Committee on Consumer Products

SCCP

# OPINION ON

# the Presence and Release of Nitrosamines and Nitrosatable Compounds from Rubber Balloons

The SCCP adopted this opinion at its 14th plenary of 18 December 2007

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 Products (SCCP), 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 Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).

In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.



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## 1. BACKGROUND

Nitrosamines are a class of chemical compounds with the generic chemical structure R2N-N=O. They are produced under certain conditions (acidic pH, high temperature, presence of certain reducing agents) in a variety of media (products, biological systems, air, etc) when nitrites react with the so called nitrosatable substances, mainly secondary amines. They have been detected as contaminants in a number of products including foods, beer, tobacco products, rubber products, and cosmetics. There is no publicly documented case of intentional addition or functional use of nitrosamines in consumer food or non food products.

From the toxicological point of view, the genotoxic carcinogenic action of some nitrosamines in animals and their probable link with human carcinogenesis is the most relevant end point. The two most common nitrosamines, N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) are classified by IARC and the EU as category 2 carcinogens (CMR cat 2).

In the EU, specific limits have been established for the presence and release of nitrosamines and nitrosatable substances from elastomer or rubber teats (93/11/EEC) and in alkyl and alkanolamines used in cosmetics (2003/83/EEC).

Concerning rubber, the formation of nitrosamines has been shown to occur when certain types of vulcanisation accelerators are used. Publicly available information from the rubber industry indicates that nitrosamine formation can be avoided if the accelerators are replaced by others which do not contain nitrosatable substances. Recently, research in Germany and the Netherlands has shown that nitrosamines and nitrosatable compounds are released when children's rubber balloons are extracted with artificial saliva to simulate the conditions of mouth blowing of balloons by children. Similar results have shown the release of nitrosamines from condoms. Research into other types of rubber products (gloves, rubber bands, erasers) has not been reported in the public domain.

On the basis of the findings in balloons, the German Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) and the Federal Institute for Risk Assessment (BfR) and the Dutch National Institute for Health and the Environment (RIVM) conducted risk assessments on the potential health risks from the release of nitrosamines in balloons. The conclusions of the risk assessments agreed that the release of nitrosamines from balloons at the reported levels do not pose reasons for concern provided the released amounts were relatively low and on the basis of assumptions on the amount of time children mouth balloons. The BgVV and BfR however, concluded that in the case of very high release as observed in the German study there may be reasons for concern. In light of these conclusions and the fact that nitrosamines are genotoxic carcinogens and therefore exposure should be reduced to the absolute minimum, the public administrations in both countries proceeded with precautionary measures. In the Netherlands, the authorities are to require balloons to carry a warning statement ("Warning: For safety reasons do not place in the mouth and blow only with a balloon pump') and in Germany guidelines are to be proposed setting limits for the content and release for nitrosamines and nitrosatable substances in rubber balloons.

As the Commission is aware of both national measures and public authorities have urged a review of the issue, we consider that it is appropriate to seek the advice of the Scientific Committee on Consumer Products concerning any potential consumer health implications when children may be exposed to nitrosamines that are released from balloons when children put them in their mouths (to blow them or simply to mouth the blowing pat of fully or partly inflated balloons) or simply when they lick them. Although specific research into the mouthing behaviour of children with balloons is lacking, published evidence shows that balloons are one of the most common toy items children above the age of 6 months and up to 4 years of age, put in their mouth (Smith A.S and B. Norris. 2003 Reducing the risk of choking hazards: mouthing behaviour of children aged 1 month to 5 years. Injury Control and Safety promotion 10:145-154).

## 2. TERMS OF REFERENCE

The Committee is requested to:

1. *Critically review the evidence concerning the migration of nitrosamines from balloons and the risk assessments conducted by the RIVM and BgVV and BfR on the potential risks arising from the exposure of young children (ages 6 months to 4 years).*

2. *In light of its response to question 1, pronounce itself as to whether there may be reasons for concern arising from the exposure of young children to nitrosamines when young children mouth and/or lick balloons. In elaborating its point of view, the Committee is asked to take into account known/published exposures of young children to nitrosamines from other known sources of exposure (food and non food products, environment, etc) and previous or ongoing assessments of nitrosamine exposure (e.g. SCF opinions or work by EFSA panels).*

3. *In light of its response to question 2, assess whether a limit of nitrosamines and nitrosatable compounds can be established that will lead to exposure of young children to balloons not giving reasons for health concerns (e.g. the 0.05 mg of nitrosamines and 1.0 mg N-nitrosatable compounds per kg rubber recently proposed for balloons by the Federal Republic of Germany). In answering this question, consideration should also be given to other sources of nitrosamines and nitrosatable compounds than rubber.*

4. *Identify any additional investigative work that needs to be done concerning both the specific issue of nitrosamines in balloons and the presence and release of nitrosamines from other rubber or non-rubber consumer products (non-food and food) resulting in eventual consumer exposure, that would enable an integrated risk assessment to be conducted concerning the total children exposure to nitrosamine from all known sources*.

## 3. OPINION

This opinion refers to the exposure to nitrosamines via balloons.

The nitrosamines can be released during blowing or mouthing balloons. Both children and adults will blow balloons, although it is expected that the exposure duration will be longer for children then for adults.

In generally, especially young children will have difficulties blowing balloons, however, they like to try, and therefore they will have substantially longer oral contact with balloons than adults.

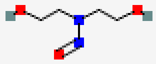
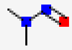
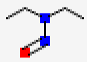
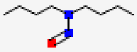
Therefore, this opinion focuses on children. By performing the risk assessment for children, adults are automatically included in the exposure scenario. In addition, children are generally also considered more vulnerable for the effects of chemicals, again indicating that this is the most relevant sub population to consider in this opinion.

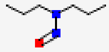
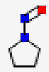
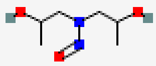
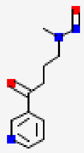
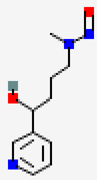
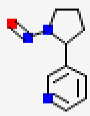
### 3.1. General Information

3.1.1. Physicochemical properties of nitrosamines

Nitrosamines (N-nitroso di-n-alkanol amines (NDAA)) are a large group of chemical compounds with the generic chemical structure R2N-N=O. There are more than 300 different nitrosamines, of which the most common ones are presented in Table 1, with CAS number, formula and structure. Also the classification of these agents according to IARC and, when available, the EU is reported.

Table 1: Overview of the most common nitrosamines to which humans are exposed

| Abbrev. | Full name | CAS-number | Formula* | Structure* | IARC/ EU classification |
|---|---|---|---|---|---|
| NDELA | N-nitroso diethanol amine | 1116-54-7 | $C_4H_{10}N_2O_3$ |  | 2B / 2 |
| NDMA | N-nitroso dimethyl amine | 62-75-9 | $C_2H_6N_2O$ |  | 2A / 2 |
| NDEA | N-nitrosodi-ethylamine | 55-18-5 | $C_4H_{10}N_2O$ |  | 2A |
| NDBA | N-nitrosodi-n-butylamine | 924-16-3 | $C_8H_{18}N_2O$ |  | 2B |

| Abbrev. | Full name | CAS-number | Formula* | Structure* | IARC/ EU classification |
|---|---|---|---|---|---|
| NDPA | N-nitrosodi-n-propylamine | 621-64-7 | $C_6H_{14}N_2O$ |  | 2B / 2 |
| NMOR | N-nitroso morpholine | 59-89-2 | $C_4H_8N_2O_2$ |  | 2B |
| NMEA | N-nitroso-methyl ethylamine | 10595-95-6 | $C_3H_8N_2O$ |  | 2B |
| NPIP | N-nitrosopiperidine | 100-75-4 | $C_5H_{10}N_2O$ |  | 2B |
| NPYR | N-nitrosopyrrolidine | 930-55-2 | $C_4H_8N_2O$ |  | 2B |
| NDiPLA | N-nitroso diisopropanol amine | 53609-64-6 | $C_6H_{14}N_2O_3$ |  | N.E*. |
| NNK | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone | 64091-91-4 | $C_{10}H_{13}N_3O_2$ |  | 1 |
| NNAL | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol | 76014-81-8 | $C_{10}H_{15}N_3O_2$ |  | N.E |
| NNN | N'-nitrosonornicotine | 16543-55-8 | $C_9H_{11}N_3O$ |  | N.E.<br>1 |

* N.E. not evaluated by IARC or EU

Apart from the mentioned carcinogenic N-nitrosamines there is also a class of less dangerous, non-carcinogenic nitrosamines. Members of this category are N-nitroso-methyl-tert-butylamine, N-nitroso-dibenzylamine (NDBzA), N-nitroso-dicyclohexylamine, N-nitrosoethyl-tert-butylamine, N-nitrosodiallylamine, N-nitroso-proline, 3-(N-nitroso-methylamino)-pyridine, 4-(N-nitroso-methylamino)-pyridine, and N,N'-dinitroso-pentamethylentetramine (BAuA TRGS 552, 2007).

Some additional characteristics for NDMA, the nitrosamine described in most detail (http://www.epa.gov/ttn/atw/hlthef/nitrosod.html), are:

- Molecular weight of 74.08 g/mol
- It is a yellow, oily liquid that is very soluble in water
- It has a faint characteristic odour; the odour threshold has not been established.
- The log octanol/water partition coefficient (log $K_{ow}$) is 0.57 and the vapour pressure is 2.7 mm Hg at 20°C.

Nitrosatable substances (or nitrosamine precursors) are substances which can be converted into nitrosamines by reaction with nitrosating agents such as nitrite and/ or nitrogen oxides. Endogenous formation of N-nitroso compounds occurs via nitrosation (by nitrite derived from nitrate) of dietary ureas, guanidines, amides, amino acids, and (primary, secondary and aromatic) amines (Shephard et al, 1987a).

### 3.1.2 Presence of nitrosamines and precursors

N-nitrosamines and/or nitrosatable substances are present, usually in trace quantities, in various environmental media such as tobacco and tobacco smoke, in certain food products such as beer, cheese, fish and cured meat products, in cosmetics, in drugs, pesticides, indoor air and often in relatively high concentrations in certain occupational conditions, especially in the rubber and metalworking industries. N-nitrosamines and precursors that are present in rubber products originate from certain accelerators (carbamates) used for the vulcanization of rubber. In general, N-nitroso dimethyl amine (NDMA) is most frequently measured as it is present in tobacco smoke, food, cosmetics, rubber products, pesticides and in several other potential sources of exposure such as interior air of new cars, alkylamine drugs and tanneries/dyes (ATSDR, 1989). The nitrosamines NDELA, NDiPLA and NMOR are frequently detected in cosmetics (VWA, 2004), whereas NNK, NNAL and NNN are tobacco-specific (Brunnemann and Hoffmann, 1991).

### 3.1.3 Toxicology of nitrosamines

Most toxicological assessments of nitrosamines focus on their carcinogenic and mutagenic properties. Little is known on other toxicological endpoints (see US EPA website). Only for NDMA, a full EU classification is available:

- Carc. Cat. 2; R45 (may cause cancer)
- T+; R26 (Very toxic by inhalation)
- T; R25-48/23/24/25 (Also toxic: danger of serious damages to health by prolonged exposure through inhalation, in contact with skin and if swallowed)

Several of the nitrosamines consumers are exposed to have been evaluated by the Agency for Research on Cancer (IARC) as Group 1: carcinogenic to humans, Group 2A: probably carcinogenic to humans or as Group 2B: possibly carcinogenic to humans (see Table 1 and the following webpage of IPCS INCHEM: http://www.inchem.org/pages/iarc.html). According to the EU, some nitrosamines (see Table 1) are classified as Category 2 carcinogenic agents (substances which are to be regarded as carcinogenic to man, because on the basis of sufficient results of long-term animal tests or indications based on animal tests and epidemiological studies it is to be assumed that they make a substantial contribution to the risk of cancer; EC/67/548). Paragraph 15a of the Hazardous Substances Ordinance provides that workers may not be exposed to these substances. Pursuant to § 35

of that Ordinance, preparations containing ≥ 0.0001% (1 ppm, 1 mg/kg) of these substances are deemed to be carcinogenic. These preparations must not be supplied to the private final consumer (Chemicals Prohibition Ordinance — annex to § 1, section 20). Since nitrosatable substances can be converted into carcinogenic nitrosamines, as mentioned above, they can form a cancer risk too.
More than 300 N-nitroso compounds have been extensively tested in 40 different animal species and caused cancer in everyone of them, both after respiratory and oral exposure (the dermal route was not tested). Since N-nitrosamines are converted by oxidative enzyme systems into substances that cause DNA mutations, which are thought to initiate carcinogenesis, they are mostly systemically acting genotoxic carcinogens. Using rat TD50-values (the chronic dose-rate in mg/kg body wt/day which would induce tumours in half the test animals at the end of a standard lifespan for the species), the different N-nitroso compounds can be ranked according to carcinogenic potency (taken from the Carcinogenic Potency Database, CPDB) as a starting point (Gold et al, 1993). The carcinogenic potency between different nitrosamines shows a wide variation, with a factor 15.000 between the most potent (NDEA; TD50 of 7.87 x $10^{-3}$ mg/kg BW/day) and the least potent carcinogen (NDP(h)A; TD50 of 116 mg/kg BW/day). These differences in carcinogenic potency only give an impression of the order of magnitude in potency differences and are not directly interpretable in terms of additional cancer risk, since the TD50 depends on the background incidence of the critical tumour. Since NDMA appears to be present in all potential sources (food, cosmetics, and rubber products) and is most commonly detected, this individual nitrosamine is often chosen as a reference nitrosamine in toxicological studies. NDMA has a high carcinogenic potency (TD50 of 58.7 x $10^{-3}$ mg/kg BW/day), which can lead to an overestimation of the risk connected to exposure to nitrosamines in general.

The carcinogenicity of NDMA has been evaluated by WHO (WHO, 2002), Dutch Health Council (Health Council of the Netherlands, 1999), DFG (DFG, 1999), RIVM (Speijers et al., 1989), ATSDR (ATSDR, 1989) and IARC (IARC, 1972a, IARC, 1978a). The description below is largely based on the most recent evaluation by WHO (WHO, 2002; Health Council of the Netherlands, 1999). NDMA has been tested in rats by oral administration via drinking water, gavage and diet and the main target organ upon oral exposure is the liver, but also lung and kidney tumours have been found. A comprehensive oral long-term study of Peto and co-workers (Peto et al, 1991a; 1991b) in which they studied the dose-response relationship for the effects of NDMA on various types of liver cancer by exposing rats to 16 different doses of NDMA in drinking water, led to an additional lifetime cancer risk of 5.0 x $10^{-3}$ per µg NDMA/ kg body weight/day (life span conditions). Inhalation studies resulted in tumours mainly in the nasal cavity, and respiratory tract. The most sensitive and reliable inhalation study as performed by Klein et al. (cited in Health Council of the Netherlands, 1999), in which female rats were exposed to atmospheres with 4 different doses of NDMA (0, 0.04, 0.2 and 1.0 ppm, corresponding to 120, 300 and 3000 µg/m3) four times per week, 4-5 hrs per day, for 207 days, resulted in an estimated tumour incidence of 0.1 per µg/m3 (life span conditions). No dermal studies are performed to derive a cancer risk value for NDMA.

Information on the dose-response association between human nitrosamine exposure and risk of cancer is mainly provided by two types of exposure routes, i.e. occupational exposure through inhalation and exposure in the diet. Occupational exposure led to stomach, oesophagus, lip, oral cavity, pharynx and lung cancer (Cocco, 1994; Cocco, 1998; Li, 2002; Straif, 2000; Sullivan, 1998). However, the available evidence on occupational exposure and risk for cancer is most convincing for upper gastrointestinal tract cancers (Straif, 2000; Sullivan, 1998). In both studies, however, no control of confounding factors for upper gastrointestinal tract cancer such as smoking and alcohol consumption has been carried out. Exposure to nitrosamines in the diet occurs mostly via cured meets and beer, as was measured by habitual dietary intake by a food frequency questionnaire or diet history in different cohort and case-control studies (Larsson, 2006; Ward, 2000; Knekt, 1999; DeStefani, 1998; Wilkens, 1996; Pobel, 1995; LaVecchia, 1995). Nitrosamine (NDMA) contents of the food were calculated using published tables or values. In 4 out of 5 studies, a positive association between NDMA intake and risk of stomach cancer was found. Other cancer outcomes, nasopharyngeal, colorectal, head & neck, and urinary tract, were investigated in one study each. Only for colorectal cancer, an association with NDMA intake was found (Knekt, 1999). Furthermore, in previous studies a clear association was found for colorectal cancer and cured meat intake (Sandhu, 2001). Quantification of a human dose response association was only possible for one occupational study (Straif et al., 2000), but not for one of the dietary studies.

### 3.1.4. Legal aspects of nitrosamines and nitrosatable substances

Balloons are toys and must comply with the requirements of the toys directive 88/378/EEC. According to Article 2 No. 1 of this directive toys may be placed on the market only if they do not jeopardize the safety and/or health of users or third parties when they are used as intended or in a foreseeable way, bearing in mind the normal behaviour of children. In Annex II the essential requirements for toys are compiled. II Particular risks No. 3 summarizes the requirements regarding chemical properties, i.e. toys must be so designed and constructed that they do not present health hazard.
Although balloons are not intended to be put into the mouth by babies and young children, it is considered to be very likely. In fact, as already mentioned in the background, balloons are one of the most common toy items that are mouthed by children above the age of 6 months and up to 4 years of age (Smith and Norris, 2003).

The migration limits for nitrosamines and nitrosatable substances in rubber teats and soothers, as regulated in European directive (93/11/EEC) (Commission Directive, 1993), can therefore be used to evaluate the found migration levels from balloons. These migration limits for nitrosamines and nitrosatable substances from rubber teats and soothers are:

N-nitrosamines, in total: 10 µg/ kg rubber
Nitrosatable substances, in total, determined as N-nitrosamines: 100 µg/ kg rubber

The migration limits are based on detection limits and not on toxicological evaluation, as for genotoxic carcinogenic substances, no safe level exists.
As high levels of N-nitrosamines in balloons can be avoided by using state-of-the-art technology, high exposure to N-nitrosamines is unjustifiable. The plastics Committee of the BfR (previously BgVV) in Germany recommended incorporating balloons (and other daily-use goods) into a special category defined in the BfR Recommendation XXI, resulting in a specific limit for balloons. According to this Recommendation, the release of N-nitrosatable substances from balloons should be limited to 5 µg/ $dm^2$, referred to the surface area of the balloon (BgVV 2002). Based upon exposure considerations and in view of the market situation at that time, BfR in 2004 discussed a nitrosamine limit of 200 µg/ kg or 0.5 µg/ $dm^2$. In 2007, a draft law has been framed by the Federal Republic of Germany in which new limits for nitrosamines and nitrosatable substances in balloons were proposed: 50 µg /kg and 1000 µg /kg respectively (14$^{th}$ Order amending the Essential Commodities Order, 2006).
In cosmetics, nitrosamines are banned (Annex II/411); the limit of 50 µg/kg, given in the Cosmetics Directive, refers to traces of nitrosamines.

An overview of the legislative proposals and measures is given in Table 2.

Table 2: Overview of legislative proposals and measures with regard to nitrosamines

| **Legislation** | **Product** | **Nitrosamines** | **Nitrosatable compounds** |
|---|---|---|---|
| Directive 93/11/EEC<br>Food and Commodities Act | Teats and Soothers | 10 µg/kg | 100 µg/kg<br>0.25 µg/ $dm^2$ |
| BgVV Recommendation XXI (2002) | Balloons | 10 µg/kg | 5 µg/ $dm^2$ |
| BfR proposal (2004) | Balloons | 200 µg /kg<br>0.5 µg/$dm^2$ | 2000 µg /kg<br>5 µg/$dm^2$ |

| Legislation | Product | Nitrosamines | Nitrosatable compounds |
|---|---|---|---|
| German draft law 2007 | Balloons | 50 µg /kg | 1000 µg /kg |
| Directive 76/768/EEC as amended | Cosmetics | 50 µg /kg (NDELA) | |

## 3.2 Exposure Information

3.2.1 Levels of nitrosamines and nitrosatable substances in balloons

3.2.1.1 Design of migration experiments

For determination of the migration of nitrosamines and nitrosatable substances from teats and soothers, a standardized protocol was developed (EN 12868). This protocol is, with a few adaptations, also applicable for testing of balloons. First, the migration time is shortened from 24 hour to 1 hour, as for children the exposure to balloons is much shorter than the exposure to teats and soothers. Interestingly, 45% of the total migration has taken place within the first hour (KvW 2002). Secondly, in contrast to teats and soothers, the balloons are not boiled for 10 minutes prior to testing. For quality assurance of the obtained data, all measurements are performed under 'Good Laboratory Practice" (GLP) conditions.
In a test conducted by the Laboratory for Food and Residue Analyses of RIVM in 2002, balloons from the Dutch market were sampled in the South-West regions of the Netherlands, covering approximately 75% of the brands on the Dutch balloon market. For the migration analysis the test protocol used was similar to EN12868. All the balloons in a bag (from 1 package) were cut into pieces of approximately 1 $cm^2$. From these snippings, a representative subsample of 5 grams was taken to measure migration of nitrosamines and nitrosatable substances in the prescribed, nitrite containing saliva simulant, during 1 hour at 40°C. For determination of nitrosatable substances, these are converted into nitrosamines by acidification of the aliquot with hydrochloric acid. Subsequently the nitrosamines are extracted from the solution and determined (Commission Directive 93/11/EC).
The detection limit (3 times the noise level) varied for the different nitrosamines from 0.5-1.7 µg/ kg rubber. For nitrosatable substances, the detection limit varied from 3.2-11 µg/ kg rubber.

3.2.1.2 Levels found in balloons

In the past 5 years, the release of nitrosamines and nitrosatable compounds (precursors) from balloons was determined several times by the Laboratory for Food and Residue Analyses of RIVM. At the first time in July 2002 (KvW, 2002), the following individual nitrosamines were detected in balloons: NDMA, NDEA, NDBA, NDBzA, N-nitrosodiisononylamine (NDiNA), N-nitrosodiisodecylamine (NDiDA), and NMOR, with NDMA (in 96% of the samples), NDBA (61%) and NDiNA (16%) as the most frequently detected ones. As regards nitrosatable compounds, the main precursors were found for again NDMA (in 96% of the samples), NDBA (66%) and NDiDA (20%). The maximum release of NDMA, NDEA and NDBA from nitrosatable substances was 2.82, 2.26, and 4.74 mg/ kg/ hour respectively. On average, the total of all N-nitrosamines measured was 0.13 mg /kg balloon material per hour, and total nitrosatable substances amounted to be 1.51 mg/ kg/ hr. Peak values were 0.63 mg/kg nitrosamines and 5.73 mg/kg nitrosatable substances per hour. Only 1 balloon package in this test complied with the migration limits imposed on teats and soothers (KvW, 2002).
In June and July 2004, N-nitrosamine measurements were repeated by the same laboratory in 58 balloons sampled at the importers of the balloons, to investigate whether there was any improvement visible in 2 years of time (VWA, 2005). Again, the nitrosamines and nitrosatable substances most frequently found in balloons were NDMA (in 95% of the balloons tested) and NDBA (93%) and their precursors. Three other nitrosamines were found as well; N-nitrosomethylphenylamine (NMPhA), NDBzA and NDEA. The average release of nitrosamines and nitrosatable substances was 0.072 mg/kg and 0.65 mg/kg per hour, the highest release was 0.75 and 3.2 mg/kg/hr respectively, mainly from NDMA and NDBA. In comparison to 2002, a shift to a lower release of nitrosamines and nitrosatable

substances was noticeable in the distribution of these compounds. The results indicate an improvement in 2 years time, but still the majority of the balloons do not comply with the migration limits set by the German BgVV Recommendation XXI standards (38 out of 58) or with the limits for teats and soothers (50 out of 58). The 21 balloons tested under the authority of Greenpeace (by two recognized special laboratories following the protocol recommended by BfR) resulted in mean migration levels of nitrosamines in the same order of magnitude. Mean and maximum migration levels for total nitrosamines and nitrosatable substances were 0.79/ 4.64 and 1.27/ 3.2 mg/kg/hr respectively. Only 4 balloons (19%) contained nitrosamine levels below the limit of 10 µg/kg rubber while the recommended limit of 5 µg nitrosatable substances /$dm^2$ was exceeded by 3 balloons (Greenpeace, 2004). Altkofer and coworkers described determination of nitrosamine migration levels in 30 balloon batches from 2 different sampling moments (2001 and 2003). Migration levels of NDMA, NDBA and NDEA were most frequently found and varied between <10 to 380 µg/kg rubber per hour. Nitosatable substances were found at a migration level of < 10 to 4300 µg/kg/ hr, a maximum that corresponds to 12.4 µg/$dm^2$/h (Altkofer et al, 2005). Also in this study the different balloons analysed show a large variation of nitrosamine migration rates as is emphasized by the following distribution figure.

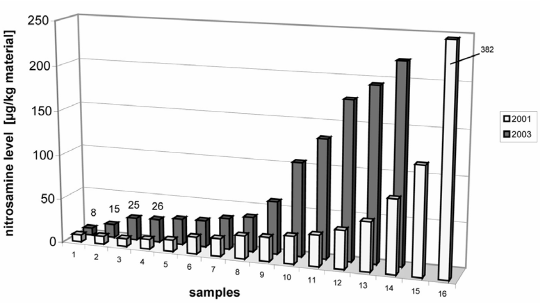



Figure 1: Distribution of nitrosamine levels/ hr found in 30 different rubber balloon batches

Recently, a study from Denmark became available. Four Balloons were analysed for nitrosamines and nitrosatable substances according to EN 12868. The level of nitrosamines in all four balloons was below the proposed level in the German draft law of 0.2 mg/kg. Only one out of four balloons complied with the proposed German level for nitrosatable substances of 2 mg/kg (levels in other three varied between 2.8 and 10.9 mg/kg) (Nilsson, 2007).

3.2.1.3. Average exposure as a result of mouthing balloons

The exposure to nitrosamine levels in balloons can be calculated via the following equation:

$$Exp = \frac{t * \left[ \left( LR_{NA} * pos_{NA} + CF * LR_{NC} * pos_{NC} \right) * W_N \right]}{W_C} \quad \text{(Equation 1)}$$

Where:

| | | |
|---|---|---|
| *Exp* | = | average exposure (ng NA/kg bodyweight per day) |
| t | = | mouthing time per day (min) |
| posx | = | proportion of balloons with detectable nitrosamines or nitrosatable compounds, respectively |
| $LR_{NA}$ | = | Average Leaching Rate for nitrosamines (µg/kg rubber product per min) |
| $LR_{NC}$ | = | Average Leaching Rate for nitrosatable compounds (µg/kg rubber product expressed per minute) |
| CF | = | correction factor; proportion of nitrosatable compounds which are converted to nitrosamines (1%; Van Leeuwen, 2003) |

$W_N$ = weight of mouthpiece (kg)
$W_C$ = weight of child (kg)

Mouthing times per day were taken from Smith and Norris (2003) and determined for three different age groups. Children of 6-12 months, 1-2 years and 2-4 years mouth respectively 31, 14,3 and 8,7 min/ day on toys including balloons. The proportion of balloons with detectable levels of nitrosamines or nitrosatable compounds was 84% based on the most recent published data (VWA, 2005). Leaching rates were on average 72 and 650 µg/kg/hr for nitrosamines and nitrosatable compounds, respectively (VWA, 2005). The weight of the balloon's mouthpiece was 270 mg. When bodyweights of 9, 12 and 15 kg are assumed for children aged 6-12 months, 1-2 years and 2-4 years, the calculated exposure for children of these different age groups is then respectively: $1.03 \times 10^{-3}$, $0.36 \times 10^{-3}$ and $0.16 \times 10^{-3}$ ng/kg BW/ day.
Note: A frequently used (worst case) assumption for the time children are mouthing toys and teats is 3 hours per day (CSTEE, 1998). When this time is used in the abovementioned equation to calculate exposure to nitrosamines out of balloons, exposure rates are respectively 6, 12 and 20 times higher. Even then the calculated exposure rates are very low (about $6 \times 10^{-3}$ ng/kg BW/day).

### 3.2.2 Levels in other sources

#### 3.2.2.1 Background exposure from food and passive smoking

Background exposure to nitrosamines occurs mainly via food and passive smoking. The foodstuffs that have been most commonly contaminated with NDMA (and other nitrosamines) can be classified into several broad groups: I) Foods preserved by the addition of nitrate/ nitrite, such as cured meat products (in particular bacon) and cheeses, since these methods of preservation introduce nitrosating species into the food. II) Foods preserved by smoking such as fish and meat products since oxides of nitrogen in the smoke act as nitrosating agents. III) Foods dried by combustion gases, such as malt, low-fat dried milk products and spices since combustion gases can contain oxides of nitrogen and IV) pickled and salt-preserved foods, particularly pickled vegetables since microbial reduction of nitrate to nitrite occurs (Environment Canada/ Health Canada, 2001). Measured NDMA concentrations in duplicate portions of adult diets were about 0.13-0.38 µg/ person/ day in 1980 and decreased to < 0.1 µg/ person/ day in 1990 (Ellen et al, 1990). Other estimations indicate that ingestion from food items amounts a few hundred nanogram per person per day (RIVM, 1989) or 0.2 µg and 0.3 µg N-nitrosamines per day for women and men, respectively (Nutrition Report of the German Nutrition Society, 1988). Simultaneous intake of amines from fish (dimethylamine) and vegetables rich in nitrate could lead to endogenous formation of nitrosamines (Vermeer et al, 2000), a mean adult fish consumer might produce 180 ng NDMA per day. Furthermore, it has been suggested by Shephard et al, that dietary ureas and aromatic amines combined with a high nitrite burden could pose as great a risk as the intake of preformed NDMA in the diet (Shephard et al, 1987 b).
For children, no exposure levels were determined in duplicate portions in the described studies. However, since the nitrosamine concentrations in cured meat (mean 0.5 µg/kg, max 3.6 µg/kg), sea food (mean 0.4 µg/kg, max 2.1 µg/kg) and cheese (mean 0.1 µg/kg, max 1.1 µg/kg) were measured and dietary habits of young children in different age groups are published recently (Boon et al, 2004), the exposure can be roughly estimated by multiplying the consumption with the measured concentrations. Children of 8-12 months old consume maximal 20 gram of meat or fish per day (Boon et al, 2004). (No data on the consumption of cheese was provided for this age group). It is assumed that for older children up to 4 years, this amount can rise to 50 gr. The nitrosamine intake of children from food is than on average 0.5 x 0.050 kg = 0.025 µg = 25 ng and in worst case maximal 3.6 x 0.050 kg = 180 ng / day for meat or fish. These levels are comparable to worst case estimates of the daily intake of NDMA in Canada, where a daily intake from food of 6.5-16 ng NDMA/kg BW/day was estimated for children of 0.5-4 years (Environment Canada/

Health Canada, 2001). When assumed that a child in this age range weighs maximal 15.5 kg, the total NDMA intake from food can rise to 100.8-248 ng/day.
The amount of NDMA endogenously formed from fish and vegetables can be calculated by for both adults and children. The mean amount of NDMA formed was 0.22 µg/ kg BW for children aged 4 years old, a factor 5 higher than for adults older than 18 years (M.J. Zeilmaker, RIVM, personal communication). This corresponds with the in general higher consumption per kg bodyweight (higher energy intake) for children. When it is assumed that the weight of a child of 4 years old is on average 15.5 kg, an amount of up to 15.5 x 0.22 = 3.41 µg NDMA can be formed out of a fish/ nitrate-rich vegetable meal (M.J. Zeilmaker, RIVM, personal communication).
For passive smoking, the contribution to nitrosamine intake is not exactly known, but is estimated to be a factor 10 higher than intake through food items. The worst case scenario for uptake of NDMA via environmental tobacco smoke (ETS) in indoor air estimated by Health Canada (21 hours breathing ETS contaminated indoor air NDMA at the maximum reported concentration of 0.24 µg NDMA/$m^3$) resulted in a concentration of 0.13 µg/kg BW/day for children of 0.5-4 years (children of this age are assumed to breathe 9.3 $m^3$ air per day). This level is a factor 4.5-16 higher than the sum of the intake through foodstuffs, water and outdoor air (0.0081-0.029 µg/kg BW/day). According to the IARC monograph 83 (2002) the levels of N-nitrosodimethylamine (NDMA) measured in the field (e.g. in workrooms, conference rooms, restaurants and bars where people smoked) are ranging from less than 10 ng/$m^3$ to 240 ng/$m^3$ (Jenkins et al., 2000 referred in IARC monograph). In unventilated offices in which 11-18 cigarettes were smoked during a 2-h period, up to 8.6 ng/$m^3$ N-nitrosodiethylamine (NDEA) and up to 13 ng/$m^3$ N-nitrosopyrrolidine (NPYR) were measured. These ETS levels can lead to an inhalatory NDMA exposure in children of 6 -144 ng/ kg BW/ day. The question is however, how relevant these areas are for children.
Taken together, the exact background exposure to nitrosamines via food and passive smoking is not well known for children in the age of 6 months to 4 years, but worst case estimates can rise up to levels of 138-159 ng/kg BW/day, and a few hundred ng up to 3 µg per person per day are found for adults.

3.2.2.2 Rubber teats and soothers

For babies and toddlers of in the age group 6 months to 4 years, additional sources for exposure to nitrosamines and nitrosatable substances are rubber teats and soothers. In 2 different Dutch retail studies, levels of nitrosamines and their precursors were measured in these products by 24 hour extraction using artificial saliva (Ellen et al, 1987; Bouma, 2003). Details of these studies are given in Table 3.

Table 3: Nitrosamine levels in bottle teats and soothers, determined by 24 hour extraction using artificial saliva, expressed in µg/kg rubber

| | Teats | | | | Soothers | | | | Source |
|---|---|---|---|---|---|---|---|---|---|
| | % positive | Mean | Min | Max | % positive | Mean | Min | Max | |
| Nitrosamines | 83 | 23.7 | 4 | 56 | 64 | 27 | 7 | 94 | Ellen, 1987 |
| Precursors | 83 | 1067 | 26 | 4900 | 64 | 1294 | 42 | 5100 | Ellen, 1987 |
| | | | | | | | | | |
| Nitrosamines | 86 | 0.43 | 0.2 | 0.7 | 60 | 1.43 | 1.3 | 1.6 | Bouma, 2003 |
| Precursors | 36 | 4.72 | 0.5 | 21 | 20 | 234 | | | Bouma, 2003 |

From these data, the average daily exposure to nitrosamines and nitrosatable substances as a result of mouthing teats and soothers can be calculated. For teats, assumptions have to be made for average drinking time, amount of bottles per day, proportion of teats with detectable nitrosamines or nitrosatable compounds, the average leaking time for both and the proportion of nitrosatable substances that are converted to nitrosamines. For soothers, the default mouthing time is very important for determination of the exposure. However, the exposure for both sources turns out to be negligible when compared to other sources and background exposure, i.e. 0.00-0.01 ng/kg/day for teats and 0.02-0.07 ng/kg/day for soothers, dependent on the age of the child and based on the most recent migration data (Bouma, 2003).

3.2.2.3 Cosmetic products

Also (children's) cosmetic products will contribute to the nitrosamine exposure of children. In a recent survey on nitrosamines (NDELA) in cosmetic products (VWA 2004, report NDCOS017/04), about 17% of the tested products ((baby) shampoo, shower gel, (baby) bath foam contained detectable NDELA levels, with the highest levels found in shampoo and shower gel (up to 945 and 992 µg/kg respectively), see also Table 4.

Table 4: Nitrosamine levels in several cosmetic products

| | % positive | Concentration µg/kg | | |
|---|---|---|---|---|
| | | **Mean** | **Min** | **Max** |
| Shampoo | 15 | 231 | 23 | 945 |
| Shower gel | 18 | 284 | 24 | 992 |
| Bath foam | 17 | 260 | | |

Source: VWA report NDCOS017/04. More recent measurements on NDELA levels in cosmetic products show the same values and trends. Detection limit of NDELA in cosmetics is 23 µg/kg product.

However, some values are exceptionally high values that largely exceed the limit, since the Directives 76/768/EEC and 92/86/EEC on cosmetics products prescribe maximal levels of 50 µg NDELA /kg product (see also Table 2). Exposure rates to nitrosamines can be calculated with the following equation when default values for frequency of use per age category, taken from the RIVM fact sheet on cosmetic products (2000, report 612810013), are taken into account.

$$Exp = \frac{Amt * fy * \%pos * Conc * DF * SP}{W * 365} \quad \text{(Equation 2)}$$

Where
*Exp* = average daily exposure (µg NA/kg bodyweight)
*Amt* = amount of cosmetic used each time (g)
*fy* = frequency per year
*% pos* = percentage of positive samples
*Conc* = mean concentration in product (µg/kg product)
*DF* = dilution factor if diluted in bath water
*SP* = skin penetration (fraction)
*W* = bodyweight (kg)

The factor 365 adjusts exposure per year to exposure per day.

However, the default values used in the fact sheet on cosmetic products are only for adults. It is assumed that baby's and infants have a different cosmetic use than adults, they are bathed more frequently. The adjusted default values for bathing frequency are for 0-6 months: 5x/ week=329/year; for 6-12 months: 4x/ week= 208/year, for 1-2 years: 3x/ week=156/year. We assumed that children between 2- 4 use 100 times a year shower gel. Suntan lotion is used 75 times (25 days per year, 3 times a day). Furthermore, the amount of cosmetic product is corrected with respectively a factor 0.26, 0.29 and 0.37 for the smaller body surface area of children of 6-12 months, 1-2 years and 2-4 years according to the General Factsheet (Bremmer et al, 2006). Skin penetration of nitrosamines is 7.7% for products directly applied to the skin and 4.3 % for products that are rinsed off, respectively (Walters et al, 1997; Brain et al, 1995). For rinse-off products also a retention factor of 0.1 is used in the calculation of the exposure values.

In Table 5, exposure rates for bathing foam, and shower gel are given by using the limit value of 50 μg/kg NDELA per product and with the assumption that 18% of the samples is NDELA positive.

3.2.2.4 Summary of exposure rates

Taken together, children in the age of 6 months to 4 years are exposed to nitrosamines mainly via food and passive smoking. The contribution of other sources to the total nitrosamine intake (including mouthing balloons) is much lower.

Table 5: Exposure to nitrosamines in ng/ kg BW/ day

| | 6-12 months | 1-2 years | 2-4 years |
|---|---|---|---|
| **Food** | | | |
| Cured meat/fish [a] | 10 (8-12 months) | 10-25 | 25-180 |
| Food[b] | 6.5-16 | | |
| | | | |
| **Passive smoking** | | | |
| Indoor air-ETS[c] | 130 | | |
| | | | |
| **Rubber products** | | | |
| Rubber teats | 0.00 | 0.00 | NA |
| Soothers | 0.07 | 0.04 | 0.02 |
| Balloons | $1.03 \times 10^{-3}$ | $0.36 \times 10^{-3}$ | $0.17 \times 10^{-3}$ |
| | | | |
| **Cosmetics[d]** | | | |
| Bathing foam | $6.6 \times 10^{-2}$ | $3.2 \times 10^{-2}$ | $1.8 \times 10^{-2}$ |
| Shower gel[e] | 5.5 | 3.5 | 2.2 |

[a] absolute values/day, not to be multiplied by BW

[b] NDMA values as reasonable worst-case estimates of daily intake in children age 0.5-4 years of the general Canadian population (Health Canada, 2001). Children of this age are assumed to weigh 15.5 kg, and breathe 9.3 $m^3$ of air per day.

[c] Environmental Tobacco Smoke exposure in children age 0.5-4 years, based on the (worst-case) assumption that the population spends 21 hrs per day breathing ETS contaminated indoor air containing NDMA at the maximum reported concentration (0.24 μg/ $m^3$) measured in a bar in USA (Health Canada, 2001).

[d] Exposure levels to NDELA in shower gel when assumed that 18% of shower gels contains the approved amount of 50 μg/kg NDELA

## 3.3. Scope of the present opinion

The present opinion is mainly based on the opinion of RIVM (RIVM, 2003) and BfR (BfR, 2004; BfR, 2003; BgVV, 2002)

3.3.1. RIVM

Following the KvW report ND1TOY01/01 on the release of nitrosamines and nitrosatable compounds (precursors) from balloons, the Inspectorate for Health Protection and Veterinary Public Health requested the Centre for Substances and Integrated Risk Assessment of RIVM in December 2002 to assess the health risk, in particular the cancer risk, for children coming into contact with these balloons.
The risk assessment is performed in the next subsequent steps, and the following variables and assumptions have been taken into account (RIVM 2003):

1. Of the test results described in KvW report ND1TOY01/01, the total migration numbers of all nitrosamines and of all 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, the maximum migration 0.63 and 5.73 mg/kg product/ hour, respectively.
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 x 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 period of one hour was calculated by multiplying maximum migration levels x weight of the mouthpiece (0.63 x 270 =170 ng/ hr). Per year, this maximum exposure to nitrosamines is 5 x 0.63 x 270 = 850 ng.
6. The maximum exposure to nitrosatable substances was calculated in the same way and was 5.73 x 270 = 1547 ng/hr.
7. Subsequently, the calculated exposure was compared with a risk specific dose (RSD) corresponding to a negligible additional cancer risk of $1:10^6$. Based on animal experiments, the RSD for NDMA was 1.5 ng/kg bodyweight per day. For children in the age of 3 (-10 years) with a mean bodyweight of 15 (to 30) kg, this corresponds to a RSD of 22 (-45) ng/day = 8.000 (- 16.0000) ng/year.
8. The highest cumulated annual exposure to nitrosamines by contact with the mouthpiece (850 ng/year) is a factor 10 (-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 x (170 + (1%  x 1547) = 5 x 185 = 925 ng/year.
10. Also the highest exposure to nitrosamines *and* nitrosatable substances is caused by contact with the mouthpiece and is still about 10 (-20) times lower than the RSD of 8.000 (–16.000) ng cumulated over 1 year.

Thus the additional lifetime cancer risk from exposure to nitrosamines from rubber balloons is considered to be negligible. In addition, it can be concluded that the mean exposure of 35 ng/h (= 0.13 x 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 $1:10^6$. The opinion of RIVM is that, based on the available migration data, the previously established cancer risks and the selected worst-case exposure scenario, it can be concluded that there is no health i.e. cancer risk for children coming into contact with nitrosamines and their precursors when playing with balloons containing these compounds. The limited available data on background exposure to nitrosamines indicate that the estimated incidental exposure of children through contact with balloons does not contribute substantially to the current total exposure to these compounds.

### 3.3.2. BfR

In 2003, also BfR conducted a risk assessment on the data as described in the KvW report ND1TOY01/01 (BfR 2003). In this assessment the following assumptions were made.

1. Exposure was assessed as a worst case scenario on the basis of the maximum migrated quantities measured for individual N-nitrosamines (summarized in Table 5).
2. A surface area approach was adopted on the data, assuming that one kilogram of uninflated balloon material corresponds to an area of 400 $dm^2$.
3. The exposure surface when a balloon is used is taken to be 10 $cm^2$.
4. When the levels of Table 6 are taken, a maximum ingestion quantity of 0.155 µg NDMA, and 0.158 µg total nitrosamines per day is calculated.

Table 6: Maximum migration rates and exposures as measured in Germany (BfR, 2003)

| | N-nitrosamine | | | Precursor | | |
|---|---|---|---|---|---|---|
| | 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 (Table 2). 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 400 square decimetres (dm²) corresponds to a balloon mass of 1 kg. Where the migrateble quantities exceed 1000 µg/kg, migrates are equivalent to preparations N-nitrosamines ≥ 0.0001% (1 ppm, 1 mg/kg), which may not, according to the chemicals legislation, be supplied to the private consumer. These high levels have been found in balloons already several times. Since high levels of nitrosamines can be avoided by using state-of-the-art technology, the resulting exposure to nitrosamines is therefore unjustifiable.

3.3.3. 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 summarized in Table 7.

Table 7: Assumptions made for risk assessments

| | RIVM | BfR |
|---|---|---|
| Mean migration level (mg/kg/hr) | Nitrosamines: 0.13<br>Precursors: 1.51 | |
| Maximum migration level (mg/kg/hr) | Nitrosamines: 0.63<br>Precursors: 5.73 | NDMA: 0.62<br>Nitrosamines: 0.63 |
| Exposure rate/ year | 5 x 1 hour | |
| Surface Area | 100 $cm^2$ | 10 $cm^2$ |
| Weight balloon | Surface: 90 mg<br>Mouthpiece: 270 mg | |
| Conversion of precursors to nitrosamines | 1% | |
| Dose associated with risk of 1 x $10^6$ | 1.5 ng/ kg BW/ day | |
| 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 in 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 x 270), a value that lies around the RSD of 22-45 ng/day. However, BfR is more concerned of the peak exposures that can occur by licking a balloon with extreme 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 µg/kg (ng/mg) x 270 mg = 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 abovementioned RSD with a factor 4-8.

### 3.3.4 Discussion

** Percentage of tested balloons exceeding the nitrosamine limits*

In previous measurements, extreme high individual nitrosamine migration levels were found in balloons in Germany. In the first official tests on balloons carried out in the Rhineland-Palatinate and Mecklenburg- Western Pomerania, migration values were measured with a maximum of 273 µg/kg/ hr for NDMA, 2394 µg/kg/ hr for NDEA, 61 µg/kg/ hr for NDBzA and 3084 µg/kg/hr for NDBA (BgVV 2002). To assess the opinion of BfR and to evaluate how often balloons are found with extreme nitrosamine levels, it is important to determine in which percentage of the balloons values of nitrosamines and/ or nitrosatable precursors are measured that exceed the migration limits. For that, the individual test results of different tests (Altkofer et al, 2005, KvW/ VWA 2002, 2005, Greenpeace 2004) have to be taken into account. In the following table, an overview is given of the number of balloons per available and published test that have nitrosamine and nitrosatable precursor levels that exceed the different migration limits.

Table 8: Overview of percentage of balloons with nitrosamine and precursor levels that exceed the limits or the 400 µg/kg value associated with a potential health hazard

| | **Nitrosamines (µg/kg)** | | | **Nitrosatable substances (µg/$dm^2$)** | | |
|---|---|---|---|---|---|---|
| | **> 10** | **> 50** | **> 400** | **> 0.25 *** | **> 2.5*** | **> 5** |
| **KvW 2002 (n= 57)** | 93% (53) | 68% (39) | 5% (3) | 98% (56) | 87% (50) | 18% (10) |
| **VWA 2005 (n= 58)** | 81% (47) | 40% (23) | 3% (2) | 84% (49) | 29% (17) | 3% (2) |
| **Greenpeace 2004 (n=21)** | 81% (17) | 29% (6) | 5% (1) | 95% (20) | 66% (14) | 19% (4) |

| | Nitrosamines (µg/kg) | | | Nitrosatable substances ($\mu g/dm^2$) | | |
|---|---|---|---|---|---|---|
| | > 10 | > 50 | > 400 | > 0.25 * | > 2.5* | > 5 |
| **Altkofer 2005 (n=16)** | 81% (13) | 19% (3) | 0% | - | - | 31% (5) |
| **(n=14)** | 93% (13) | 43% (6) | 0% | - | - | 7% (1) |

* 0.25 and 2.5 $\mu g/dm^2$ correspond to 100 and 1000 µg/kg, the limit for nitrosatable substances in teats and soothers and the new limit as proposed in the German draft law, respectively (see also Table 2).
** Absolute number of balloons is given between brackets.
- Data not available

In total (only) 6 out of 166 balloons (3.6%) recently tested exceed the nitrosamine level of 400 µg/kg, the level that BfR considers as a potential health hazard. Absolute nitrosamine levels of these balloons are 629, 529, 661, 576, 747 and 464 µg/kg, levels that do not largely exceed the 400 value. Furthermore, none of the balloons exceed the 1000 µg/kg level, equivalent to the levels which may not, according to the chemicals legislation, be supplied to the private consumer.

High levels of nitrosamines can be avoided by using state-of-the-art technology, but not much improvement has been made on this in the Netherlands in the past 5 years. Based on the 2002 results reported by KvW (report ND1TOY01/01), agreements have been made between the Inspectorate for Health Protection and Veterinary Public Health, the minister of Health, Welfare and Sports and the suppliers or importers of balloons in the Netherlands (Regulier Overleg Warenwet (ROW)) to put a warning on the labels: "Warning! For safety reasons do not take balloons in the mouth and only inflate with a balloon pump." Furthermore, it was agreed that on short term the balloons had to comply with the German limits (10 µg/kg for nitrosamines and 5 $\mu g/dm^2$ for nitrosatable substances) and on a long term they would be phased out. The VWA reported in 2005 that the market of balloons has been improved since 2002, because a lower release of nitrosamines and nitrosatable compounds out of balloons was found (VWA, 2005). However, the majority of the balloons still did not comply with the different migration limits. More analyses in the past few years (2004-2007) revealed very frequently high levels of (precursors of) nitrosamines in balloons (R. Schothorst, RIVM, personal communication).

* *Heterogenicity in nitrosamine measurements*
When interpreting the results one has to keep in mind that determination of migration levels of nitrosamines and nitrosatable substances out of balloons can be complicated for several reasons. Balloons are heterogeneous in their nitrosamine levels, and for a single measurement, 5 grams of balloon snippings are needed. Since a balloons weighs on average 3 grams, it is impossible to measure 1 single balloon. Duplex measurements of the same batch of balloons have been demonstrated to result in a 7.4 – 25.3 % difference between 3 measurements (KvW, 2002). Although the migration protocol is standardized (EN12868), levels of nitrosamines found in balloons can differ between laboratories. For instance, migration levels of balloons from the same manufacturer in the Netherlands tests were found to be lower than in German tests (BfR 2003). In addition, since nitrosamines can be formed out of nitrosatable substances during the "lifespan" of the balloon, migration levels are not homogeneous over time. This results in different levels of nitrosamines when measured at different time points and explains why, in the measurements reported by the VWA in 2005, levels of nitrosamines measured by the manufacturer were always lower than the results determined objectively by the RIVM at a later stage (VWA, 2005). For the level of nitrosatable substances it was the other way around, RIVM levels were always lower. However, variations in nitrosamine levels are not that large that extreme values can completely be attributed to analytical variations.

* *400 µg /kg as level of potential health hazard*
According to the BfR, balloons with a level ≥ 400 µg /kg are considered to be a potential health hazard; this value is based on the limit for teats and soothers (10 µg/kg). Balloons with a level of 400 µg nitrosamines/kg do not give rise to greater exposure than a soother

that complies with the Directive 93/11/EEC. In certain age categories (6 months to 2-3 years) children are mouthing soothers much more frequent than balloons. So in relation to the exposure caused by nitrosamines out of teats/soothers, the exposure to nitrosamines out of balloons is lower. Only when the factor by which the nitrosamine levels of balloons exceed the 400 µg is very large, the exposures between teats/ soothers and balloons are comparable.

* *Peak exposure to carcinogens*
On the other hand, a nitrosamine level of 400 µg/ kg gives rise to an exposure of 0.4 x 270 = 108 ng/day. When it is assumed that there is already background exposure to nitrosamines from food and passive smoking (in the same or higher order of magnitude), this level can lead to a potential health risk because of a peak exposure to nitrosamines. From animal experiments it is already well-known that short-term or single exposure to carcinogens can give rise to tumour formation (reviewed in Health Council of the Netherlands, 1994). Carcinogenicity is an endpoint that is normally observed in long-term animal experiments with the aim of establishing a virtually safe dose (VSD). In cases of incidental exposure to carcinogens or for setting acute exposure limit values, the VSD has to be adapted by using a dose rate correction factor (DRCF). This factor is defined as the factor by which the tumour incidence at long-term low dose rates is to be multiplied to derive the tumour incidence at short term high dose rates. In the past, the value of this factor has been estimated and varies between 0 and 8.3 (based on calculations from experimental studies) or between 0 and 7.1 (based on theoretical calculations). In a worst case approach or when sufficient data are lacking, a DCRF value of 10 is appropriate as default value (Health Council of the Netherlands, 1994).

* *Peak exposure to carcinogens in children*
Theoretical models for calculating a DCRF value estimate that the highest risk is theoretically associated with a peak exposure in an early life stage and involves a compound affecting an early stage of carcinogenesis (Health Council of the Netherlands, 1994). Children may also be considered as a group at extra risk for biological reasons, because of the high level of cell proliferation and developing organs. In any case children have a much longer period compared to adults, in which cancer can develop. Bos et al (2004) described a pragmatic approach for risk assessment of peak exposure to genotoxic carcinogens, with children as a subpopulation at risk. In general, assuming a human life time of 25600 days (approximately 70 years), subsequent linear extrapolation to a single 1 day exposure, gives a 1 day dose associated with an additional tumour incidence of $1 \times 10^{-6}$ of 25600 x VSD (Bos et al, 2004). In the decision tree, carcinogen exposure in children (factor 10 for subpopulation at risk) leads to a level of 2560 x VSD (Bos et al, 2004). For nitrosamines (NDMA), the VSD (RSD) was established to be 1.5 ng/kg bodyweight, leading to a level of 2560 x 1.5 = 3840 ng/kg bodyweight per day, associated with a negligible risk for peak exposure to nitrosamines in children. This factor 10 for children was justified (proven to be safe) for NDEA in a recent EPA report on the assessment of susceptibility from early-life exposure to carcinogens (EPA, 2005). The ratio of early-life to adult cancer potencies was determined for tumor development after acute NDEA exposure in different mouse strains. The median ratio for liver tumors varied between 3.3 and 36 depending on NDEA dose, sex and strain of the exposed mice (mean 18.8) with a maximum of 226 in female mice age 15 days. For lung tumor development in the same mice, the ratios are much lower (EPA, 2005).

* *Lack of additional information of exposure in children*
In order to determine whether the total exposure to nitrosamines per day is below this adapted VSD level, the sum of all potential sources of nitrosamine exposures has to be taken. For children, information is scarce or lacking making it difficult to determine the background exposure. Nitrosamine levels taken up from food are relatively well known for adults, but not for children. For instance, specific food uptake by children in Europe has only recently been determined but not yet public available (VCP, 2005). As calculated earlier from data gathered by Boon et al, children up to 4 years of age can be exposed to levels of

25 ng nitrosamines in food. However, the food uptake is only determined for children of the age of 8-12 months, and not for older children. Furthermore, 4 year old children can convert up to 3.3µg nitrosatable compounds out of a fish and nitrate-rich vegetable meal. It is not known how realistic these assumptions are; since not all meat and fish contains nitrosamines and the frequency of such a specific meal for very young children is unknown. The data of Health Canada are more informative; however, these are based on a worst-case scenario and only for 181 food items sold in Canada (Health Canada, 2001). The question arises how representative these products are for the European market.
Also data for the contribution of passive smoking to nitrosamine exposure in children are scarce. Although the calculations made by Health Canada are not very realistic and based on a 21 hr/day exposure to the highest level of NDMA ever measured in a bar, they clearly point out that passive smoking in this respect is of considerable concern. Other sources like cosmetics and teats and soothers seem to give rise to negligible additional uptake of nitrosamines per day (Table 5).

* *New limit for balloons of 50 µg/kg nitrosamines as proposed by Germany*
The approach of the German government to restrict the nitrosamine limit to 50 µg/ kg seems realistic since i) there are technical possibilities to minimalize the formation of nitrosamines in the production process of balloons (BAuA TRGS 552, 2007) and ii) thus the exposure to nitrosamines via balloons is largely avoidable. The proposed level of 50 µg/kg is acceptable, since the exposure from a balloon with a level of 50 µg/kg nitrosamines is 0.05 x 270 = 13.5 (x 5 = 67.5) ng/day, a level that is far below the calculated VSD of 3840 ng/kg BW for peak exposure to nitrosamines. From table 8, it can be seen that still a lot of examined balloons are exceeding this level, proving that there is still a need for such a limit.

* *Knowledge gaps to be filled*
Knowledge gaps to be filled by additional investigation for better risk analysis of nitrosamine exposure of young children and the contribution of mouthing balloons in this exposure are:
- investigation of the food intake of young children (different age groups 6-12 months, 1-2 years and 2-4 years) combined with
- better examination of nitrosamine levels of food ingredients (cured meat/ fish/ cheese) and of other known sources such as cosmetics.
- realistic estimation of the contribution of passive smoking, specific for children
- other sources to which children may be exposed e.g. dental elastic bands, rubberized clothing and footwear, (air valves of) beach balls, other rubber articles like erasers etc.

## 4. CONCLUSION

- The risk assessments of RIVM focussed on average exposure, whereas BfR considered peak exposure.
- Peak exposure can lead to a potential health hazard when balloons with high nitrosamine levels are mouthed by a child on a day with high background exposure. However, when a pragmatic approach is used in which the levels are compared to a level of 3840 ng/kg bodyweight per day, associated with a negligible risk for peak exposure to nitrosamines in children, exposure levels are far below this safe level.
- Food and passive smoking are the main sources for nitrosamine exposure by children. The underlying exposure assessments are not very robust or are based on a worst case scenario and crucial data are lacking. Additional investigative work with regard to exposure of children, especially on the endogenous formation of nitrosamines and on the contribution of passive smoking, is needed. Furthermore, other potential sources for nitrosamine exposure in children should be identified and taken into account.
- A limit for nitrosamine levels for balloons is recommended, since minimisation of nitrosamine formation in the production process of balloons is possible using state-of-the-art technology and thus exposure to nitrosamines via balloons is largely avoidable.

The migration level of 50 µg/kg nitrosamines results in a negligible exposure level of 13.5 ng nitrosamines per day, not contributing to a potential health risk.
- The use of vulcanisation accelerators which result in non carcinogenic nitrosamines should be encouraged.

## 5. MINORITY OPINION

Not applicable

## 6. REFERENCES


- Altkofer W, Braune S, Ellendt K, Kettl-Gromminger M, Steiner G (2005) Migration of nitrosamines from rubber products- are balloons and condoms harmful to the human health? Mol. Nutr. Food Res. 49, 235-238.
- ATSDR (1989) Toxicological Profile for N-nitrosodimethylamine.
- BAuA (Bundesanstalt fur Arbeitsschutz und Arbeitsmedicin) (2007) Technische Regeln fur Gefarhrsstoffe (TRGS) 552.
- BfR (2003) Federal Institute of Risk Assessment. Nitrosamines in Balloons.
- BfR (2004) Assessment of Nitrosamines in Balloons. Supplementary Statement from the BfR.
- BgVV (2002) Federal Institute of Health Protection of Consumers and Veterinary Medicine. Risk Assessment: N-nitrosamines in Balloons.
- Boon PE et al. (2004). Dietary habits and exposure to pesticides in Dutch infants. RIKILT report 2004.017.
- Bos PMJ, Baars, B-J, Van Raaij, MTM (2004) Risk assessment of peak exposure to genotoxic carcinogens: a pragmatic approach. Toxicol. Letters 151, 43-50.
- Bouma et al (2003) Migration of N-nitrosamines, N-nitrosatable substances and 2-mercaptobenzthiazol from baby bottle teats and soothers: a Dutch retail survey. Food.Addit.Contam. 20, 853-858.
- Bremmer et al. (2006). General fact sheet - Limiting conditions and reliability, ventilation, room size, body surface area. Updated version for ConsExpo 4. RIVM report 320104002
- Brian KR, Walter KA, James VJ, Dressler WE, Howes D, Kelling CK, Moloney SJ, Gettings SD (1995) Percutaneous penetration of dimethylnitrosamine through human skin in vitro: application from cosmetic vehicles. Food Chem Toxicol. 33, 315-322.
- Brunnemann KD, Hoffmann D (1991) Analytical studies on tobacco-specific N-nitrosamines in tobacco and tobacco smoke. Crit Rev Toxicol. 21, 235-240.
- Cocco et al. (1994) Occupational exposures as risk factors for gastric cancer in Italy. Cancer Causes and Control. 5, 241-248.
- Cocco P, Ward MH, Dosemeci M (1998) Occupational risk factors for cancer of the gastric cardia. Analysis of death certificates from 24 US states. J Occup Environ Med 40, 855-861.
- Commision Directive 93/11/EEC of March 1993 concerning the release of N-nitrosamines and N-nitrosatable substances from elastomer or rubber teats and soothers. Official Journal L 093, 17/04/1993 P. 0037-0038.
- CSTEE (1998) Opinion on Phthalate migration from soft PVC toys and child-care articles – Data made available since the 16th of June 1998, opinion expressed at the 6th CSTEE plenary meeting, Brussels, 26/27 November 1998.
- De Stefani et al (1998) Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: a case-control study in Uruguay. Nutrition and cancer. 30, 158-162.
- DFG (1999) MAK- und BAT-Werteliste 1999. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe: Weinheim, Germany.

- DGE (1988) Nutrition Report 1988 from the German Nutrition Society (Deutsche Geselschaft fur Ernahrung).
- Ellen and Sahertian (1987) N-nitrosamines and nitrosatable compounds in rubber nipples, pacifiers and other rubber and plastic commodities. IARC Sci Publ. 84, 375-376.
- Ellen et al. (1990) Dietary intakes of some essential and non-essential trace elements, nitrate, nitrite and N-nitrosamines, by Dutch adults: estimated via a 24-hour duplicate portion study. Food additives and contaminants. 7, 207-221.
- EN12868. (1999) Child use and care articles. Methods for determining the release of N-nitrosamines and N-nitrosatable substances form elastomer or rubber teats and soothers.
- Environment Canada/ Health Canada (2001) Canadian Environmental Protection Act, 1999. Priority substances list assessment report- N-Nitrosodimethylamine (NDMA). Ottawa, Ontario: Minister if Public Works and Government Services.
- European Union, Official Journal of the European Communities (2001) L 225/33.
- EPA (2005). Supplemental Guidance for assessing susceptibility from early-life exposure to carcinogens. EPA/630/R-03/003F
- Fourteenth Order amending the Essential Commodities Order by the Federal Ministry of Food, Agriculture and Consumer Protection, Germany, 2006.
- Gold LS, Manley NB, Slone TH, Garfinkel GB, Rohrbach L, Ames BN (1993) The fifth plot of the Carcinogenic Potency Database: Results of Animal Bioassays published in the General Literature through 1988 and by the National Toxicology Program through 1989. Environ. Health Perspect. 100, 65-168.
- Greenpeace Hamburg (2004). Giftige Luftballons/ Poisonous Balloons.
- Health Council of the Netherlands (1994). Risk Assessment of peak exposure to genotoxic carcinogens. Verhagen, H, Feron,VJ, Van Vliet, PW. Report A94/04.
- Health Council of the Netherlands (1999). N-Nitrosodimethylamine (NDMA). Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS).
- IARC (1972a) IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: N-Nitrosodimethylamine. Some inorganic substances, chlorinated hydrocarbons, aromatic amines, N-nitroso compounds, and natural products. IARC Monogr Eval Carcinog Risk Chem Man 1.
- IARC (1978a) IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some N-nitroso compounds. IARC Monogr Eval Carcinog Risk Chem Man 17: 1-349
- IARC (1987). Overall Evaluation of Carcinogenicity: An Update of IARC Monographs Volume 1 to 42. Supplement 7. International Agency for Research on Cancer, Lyon, France.
- IARC (2002). IARC monographs on the evaluation of the carcinogenic risk to humans: Tobacco Smoke and Involuntary Smoking. Vol 83. International Agency for Research on Cancer, Lyon, France.
- Knekt et al (1999) Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and n-nitroso compounds: a follow-up study. International Journal of cancer. 80, 852-856.
- KvW (2002). Inspectorate for Health Protection and Veterinary Public Health. Migration of Nitrosamines and Nitrosatable Substances from Balloons. Report ND1TOY01/01.
- Larsson SC, Bergkvist L, Wolk A (2006) Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women. Int J Cancer.
- LaVecchia et al (1995) Nitrosamine intake and gastric cancer risk. European Journal of Cancer prevention. 4, 469-474.
- Li K, Yu S (2002) Economic status, smoking, occupational exposure to rubber, and lung cancer: a case-cohort study. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 20, 21-28.
- Nilsson N., Analysis of chemical substances in balloons. Danish Environmental Protection Agency. Survey of Chemical Substances in Consumer Products No. 89 2007

- Peto R, et al (1991a) Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: A detailed dose-response study. Cancer Research 51, 6415-6451.
- Peto R, et al (1991b) Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or or N-nitrosodimethylamine. Cancer Research 51, 6452-6469.
- Pobel D, Riboli E, Cornee J, Hemon B, Guyader M (1995) Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France. Eur J Epidemiol 11, 67-73.
- RIVM (1989) Integrated Criteria Document Nitrate (Eds. Duijvenboode W v, Matthijsen AJCM); RIVM report 758473012.
- RIVM (2000) RIVM Factsheet Cosmetica. Bremmer HJ, Prud'homme de Lodder LCH, Van Veen, MP. Report 6128100113.
- RIVM (2003) N-Nitrosamines in Balloons: Assessment of the Health Risk for Children.
- RIVM (2006) RIVM General Fact Sheet. Bremmer HJ, Prud'homme de Lodder LCH, Van Engelen JGM. Report 320104002.
- Sandhu MS, White IR, McPherson K (2001). Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. Cancer Epidemiol.Biomarkers Prev. 10, 439-446.
- Shephard SE, Schlatter C, and Lutz WK (1987a) Model risk analysis if nitrosatable compounds in the diet as precursors of potential endogenous carcinogens. IARC Sci Publ. 84, 328-332.
- Shephard SE, Schlatter C, and Lutz WK (1987b) Assessment of the risk of formation of carcinogenic N-nitroso compounds from dietary precusors in the stomach. Food Chem. Toxicol. 25, 91-108.
- Smith SA and Norris B (2003) Reducing the Risk of Choking Hazards: Mouthing Behaviour of Children aged 1 month to 5 years. Injury Control and Safety Promotion 10, 145-154.
- Speijers, G. J. A., van Went, G. F., van Apeldoorn, et al (1989) Appendix to Report No. 758473012 Integrated Criteria Document Nitrate. Bilthoven, Netherlands, RIVM.
- Straif K, Weiland SK, Bungers M, Holthenrich D, Taeger D, Yi S, Keil U (2000) Exposure to high concentrations of nitrosamines and cancer mortality among a cohort of rubber workers. Occup Environ Med 57, 180-187.
- Sullivan PA, Eisen EA, Woskie SR et al. (1998) Mortality studies of metalworking fluid exposure in the automobile industry: VI. A case-control study of esophageal cancer. Am J Ind Med 34: 36-48.
- US-EPA (1993). N-nitrosodimethylamine, carcinogenicity assessment. IRIS (Integrated Risk Information System), 2003; US Environmental Protection Agency, Washington DC, USA. Internet: www.epa.gov/iris.
- Van Leeuwen et al. (2003) N-nitrosamines in balloons: asessment of the health risk for children. RIVM memo.
- Vermeer ITM (2000) Nitrate exposure and endogenous formation of carcinogenic nitrosamines in humans. PhD Thesis, University of Maastricht, The Netherlands, ISBN 90-9014224-X.
- VWA (2004). Survey Nitrosaminen. N-Nitrodiethanolamine (NDELA) in Cosmetica. Report nr. NDCOS017/04 (in Dutch).
- VWA (2005). Migration of N-Nitrosamines and N-Nitrosatable Substances from Latex Balloons. Report nr. ND04o063/02.
- Walters KA, Brain KR, Dressler WE, Green DM, Howes D, James VJ, Kelling CK, Watkinson AC, Gettings SD (1997). Percutaneous penetration of N-nitroso-N-methyldodecylamine through human skin in vitro: application from cosmetic vehicles. Food Chem Toxicol. 35, 705-712.
- Ward et al (2000) Dietary exposure to nitrite and nitrosamines and risk of nasopharyngeal carcinoma in Taiwan. International Journal of Cancer. Vol 86, 603-609.
- Warenwetbesluit Speelgoed (Warenwet) van 15 mei 1991. Koninklijke Vermande B.V. (Lelystad)

- WHO (2002). N-Nitrosodimethylamine, Concise International Chemical Assessment Document (CICAD) 38, www.inchem.org/pages/cicad.
- Wilkens et al (1996) Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines and selected foods. Cancer epidemiology biomarkers and prevention. Vol 5, 161-166

**APPENDIX: Migration of nitrosamines and nitrosatable substances in 57 rubber balloons**

Table A1: Levels of individual nitrosamines and nitrosatable substances from rubber balloons as measured by the Laboratory for Food and Residue Analyses of RIVM (KvW report ND1TOY01/01, 2002)

| | N-nitrosamines (μg/kg balloon) | | | | | | | | nitrosatable substances (mg/kg balloon) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ISI nr. | NDMA | NDEA | NDBA | NDBzA | NDiNA | NDiDA | NMOR | total | NDMA | NDEA | NDBA | NDBzA | NDiNA | NDiDA | NMOR | total |
| 37619833 | 4 | | | | | | | 4 | 1.20 | | | | | | | 1.20 |
| 37619841 | 16 | | 10 | | | | | 26 | 0.43 | | 1.27 | | | | | 1.70 |
| duplo | 9 | | 8 | | | | | 17 | 0.45 | | 1.36 | | | | | 1.81 |
| 37619868 | 6 | | 29 | | | | | 36 | 0.21 | | 1.94 | | | | | 2.14 |
| 37619876 | 5 | 18 | | | | | 4 | 27 | 0.03 | 1.28 | | | | | | 1.31 |
| 37619884 | 35 | | 5 | | | | | 40 | 0.42 | | 0.02 | | | 0.18 | | 0.62 |
| duplo | 32 | | | | | | | 32 | 0.45 | | | | | 0.21 | | 0.66 |
| 37619892 | 73 | | | | | | | 73 | 0.69 | | | | | | | 0.69 |
| 37619906 | 291 | | | | | | | 291 | 1.41 | | | | | | | 1.41 |
| 37619914 | 10 | | | | | | | 10 | 1.40 | | | | | | | 1.40 |
| 37619922 | 199 | | | | | | | 199 | 1.65 | | | | | | | 1.65 |
| 37619949 | 12 | | | | | | | 12 | 0.62 | | | | | | | 0.62 |
| 37619957 | 94 | | 89 | 20 | | | | 203 | 0.72 | | 0.44 | | | 0.06 | | 1.22 |
| 37619965 | 14 | | 46 | | 54 | | | 114 | 0.63 | | 0.46 | | 0.04 | | | 1.12 |
| 37619973 | 14 | | 14 | | 14 | | | 42 | 0.48 | | 0.79 | | | 0.10 | | 1.37 |
| 37619981 | 180 | | | | | | | 180 | 1.17 | | | | | | | 1.17 |
| 37620009 | 288 | | | | | | | 288 | 1.39 | | | | | | | 1.39 |
| 37620017 | 12 | | | | | | | 12 | 1.06 | | 0.05 | 0.15 | | | | 1.27 |
| 37620092 | 61 | | 27 | | 79 | | | 166 | 0.26 | | 1.44 | | | | | 1.71 |
| 37620106 | 8 | | 11 | | | | | 18 | 0.18 | | 1.40 | | | | | 1.58 |
| 37620114 | 97 | | | | | | | 97 | 1.43 | | | | | | | 1.43 |
| 37620122 | 6 | | | | | | | 6 | 1.49 | | 0.03 | | | | | 1.52 |
| 37620149 | 33 | | 92 | | | | | 125 | 0.64 | | 0.53 | | | 0.05 | | 1.22 |
| 37620157 | 186 | | 103 | | | | | 289 | 0.94 | | 0.37 | | | | | 1.32 |
| duplo | 158 | | 112 | | | | | 270 | 0.89 | | 0.45 | | | | | 1.34 |
| 37620165 | 32 | | 150 | | | | | 182 | 0.81 | | 0.49 | | | 0.16 | | 1.46 |
| 37620173 | 66 | | 22 | | 56 | | | 144 | 2.82 | | 0.51 | | | | | 3.32 |
| 37620181 | 14 | | 52 | | | 36 | | 102 | 0.81 | | 0.38 | | | 0.06 | | 1.25 |
| 37620203 | 30 | | | | | | | 30 | 0.48 | | 0.46 | | | 0.05 | | 0.99 |
| 37620211 | 3 | | 53 | | | | | 56 | 0.70 | | | | | 0.23 | | 0.93 |
| 37620238 | 21 | | 12 | 54 | | | | 86 | 1.31 | | 1.10 | | | | | 2.41 |
| 37620246 | | | 5 | | 34 | | | 39 | 1.27 | | 0.08 | 0.66 | | | | 2.01 |
| 37620254 | | 10 | 57 | | | | | 66 | | 2.26 | 3.45 | | | | | 5.73 |
| 37620262 | 19 | | 126 | | | | | 145 | 0.17 | 1.36 | | | | | | 1.53 |

| | N-nitrosamines (µg/kg balloon) | | | | | | | | nitrosatable substances (mg/kg balloon) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ISI nr. | NDMA | NDEA | NDBA | NDBzA | NDiNA | NDiDA | NMOR | total | NDMA | NDEA | NDBA | NDBzA | NDiNA | NDiDA | NMOR | total |
| duplo | 15 | | 82 | | | | | 96 | 0.19 | | 1.59 | | | | | 1.78 |
| 37620289 | 132 | | | | | | | 132 | 0.74 | | | | | | | 0.74 |
| 37620297 | 18 | | 11 | | | | | 29 | 0.32 | | 0.51 | | | | | 0.83 |
| 37620319 | 56 | | 40 | | | | | 96 | 0.40 | | 1.73 | | | | | 2.13 |
| 37620327 | 80 | | | | | | | 80 | 0.91 | | 0.02 | | | | | 0.93 |
| 37620335 | 130 | | | | | | | 130 | 1.00 | | | | | | | 1.00 |
| 37620343 | 214 | | | | | | | 214 | 1.38 | | | | | | | 1.38 |
| 37620351 | 21 | | | | | | | 21 | 0.44 | | | | | | | 0.44 |
| 37620378 | 622 | 7 | | | | | | 629 | 1.73 | | | | | | | 1.73 |
| 37620386 | 356 | | | | | | | 356 | 1.66 | | 0.06 | | | | | 1.72 |
| duplo | 282 | | | | | | | 282 | 1.26 | | | | | | | 1.26 |
| 37620394 | 23 | | 19 | | | | | 42 | 0.45 | | 1.72 | | | | | 2.17 |
| duplo | 22 | | 15 | | | | | 36 | 0.40 | | 1.22 | | | | | 1.62 |
| 37620408 | 9 | | 19 | | | | | 27 | 0.39 | | 1.27 | | | | | 1.65 |
| 37620416 | 3 | | 35 | | | | | 38 | 0.19 | | 0.37 | | | | | 0.56 |
| 37620424 | 8 | 67 | | | 51 | | | 127 | 0.56 | | 0.31 | | | | | 0.87 |
| 37620432 | 24 | | 16 | | 20 | 12 | | 72 | 0.52 | | 0.05 | | | 0.60 | | 1.17 |
| 37620459 | 19 | | 125 | | | | | 144 | 0.44 | | 0.63 | | | | | 1.07 |
| 37620467 | 100 | | 5 | 18 | | 11 | | 134 | 0.62 | | 0.05 | | | 0.56 | | 1.24 |
| 37620475 | 9 | | 13 | | | | | 22 | 0.27 | | 1.02 | | | | | 1.29 |
| 37620483 | 15 | | 51 | | | | | 65 | 0.23 | | 1.12 | | | | | 1.35 |
| duplo | 17 | | 58 | | | | | 75 | 0.28 | | 1.18 | | | | | 1.46 |
| 37620491 | 3 | | | | | | | 3 | 0.07 | | | | | | | 0.07 |
| 37620505 | 6 | | 17 | | | | | 23 | 0.58 | | 0.10 | | | 0.16 | | 0.84 |
| 37620513 | 238 | | 40 | 59 | | | | 337 | 0.73 | | 0.33 | | | | | 1.05 |
| 37620521 | 52 | | 102 | | | | | 154 | 0.73 | | 0.68 | | | | | 1.40 |
| 37620548 | 58 | | 471 | | | | | 529 | 0.20 | | 4.73 | | | | | 4.93 |
| 37620556 | 465 | | 87 | | 110 | | | 661 | 2.22 | | 0.44 | | | | | 2.66 |
| 37620564 | 95 | | 76 | | 190 | | | 361 | 1.56 | | 0.47 | | 0.18 | | | 2.20 |
| 37620572 | 24 | | 23 | | | | | 47 | 0.76 | | 1.16 | | | | 0.04 | 1.96 |