

## **Risk assessment of N-nitrosamines in balloons**

Expert Opinion, 11 April 2002

### **1. Problem**

Various starting substances and additives are needed to produce consumer products based on natural and synthetic rubber. They include vulcanisation accelerators from the group of dithiocarbamates and thiurames which are converted during the vulcanisation process into N-nitrosamines and nitrosatable amines. Migratable levels of N-nitrosamines and nitrosatable amines have been repeatedly detected in official examinations of balloons in recent years. The following compounds were found: dimethylnitrosamine, diethylnitrosamine, dibutylnitrosamine and the amines which can form these nitrosamines. A health assessment is undertaken here of these levels and measures are proposed for precautionary consumer health protection. The basis for health assessment is firstly the toxic potency which can be established in animal experiments and secondly the estimation of exposure. Furthermore, other aspects like species differences and the special sensitivity of children to some specific noxae must be taken into account.

### **2. Result**

During the production of balloons made of rubber N-nitrosamines and nitrosatable amines may be formed from the vulcanisation accelerators used. Most N-nitrosamines are seen as genotoxic carcinogens. For substances of this kind the demand should be formulated for consumer exposure to be minimised in line with the technological state of the art. According to BgVV Recommendation XXI balloons must comply with the following guidance values: 10 µg/kg N-nitrosamines, 5 µg/dm<sup>2</sup> nitrosatable amines. In some official studies far higher migratable levels of dimethyl-, diethyl- and dibutylnitrosamine were found.

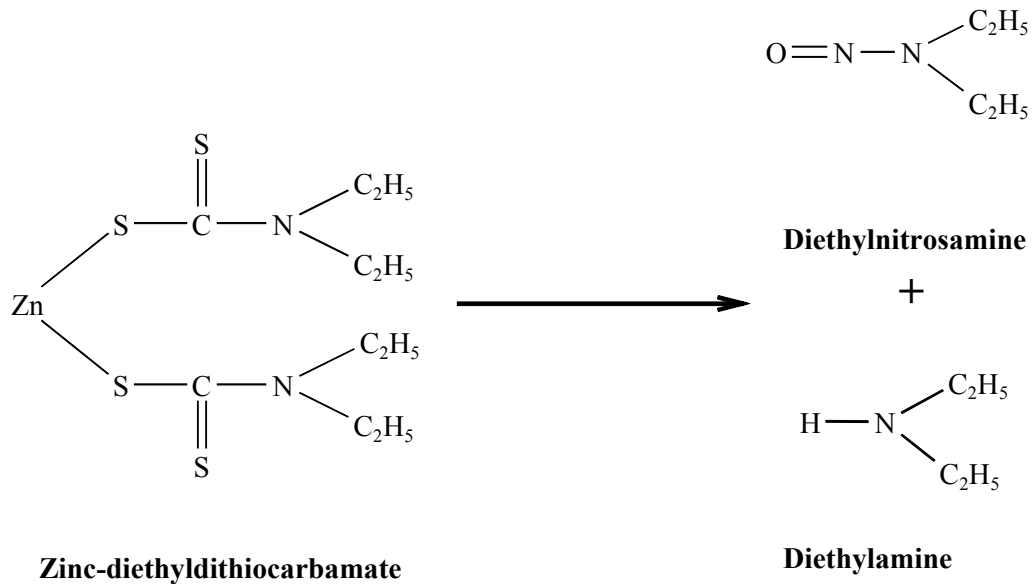
In the opinion of BgVV balloons that exceed the value of 400 µg/kg N-nitrosamines are in violation of the Ordinance on the safety of toys according to which the use of toys must be safe. In the case of migratable levels upwards of 1000 µg/kg the migrates correspond to preparations of N-nitrosamines of  $\geq 0.0001$  % (1 ppm, 1 mg/kg) which may not be sold to private end users according to chemical law. Exposure to balloons of this nature could be the same as dietary N-nitrosamine exposure. Given the particularly sensitive risk group children in this case and the additivity of the carcinogenic effect observed in animal experiments, a propensity to harm health cannot be ruled out.

BgVV is of the opinion that the migratable levels of N-nitrosamines and nitrosatable substances should be minimised in line with the technological state of the art in accordance with the demands in BgVV Recommendation XXI. However as this recommendation is obviously not complied with on many occasions, we believe statutory regulation is necessary. This demand also enjoys the explicit backing of the Plastics Committee. Furthermore, we believe it is necessary to push industry to substitute problematic vulcanisation accelerators with alternatives based on so-called "safe amines" whose use does not lead to the formation of any carcinogenic N-nitrosamines or their precursors.

### 3. Reasons

#### 3.1 Risk assessment

##### 3.1.1 Agent



**Figure 1:** Formation of diethylnitrosamine and diethylamine from zinc-diethyldithiocarbamate

The use of dithiocarbamates and thiuramens as vulcanisation accelerators leads to the formation of N-nitrosamines and nitrosatable amines (see Fig. 1). Depending on the derivative used, different alkylnitrosamines and alkylamines are formed. The tests in the federal states identified high levels of the following compounds: dimethylnitrosamine, diethylnitrosamine, dibutylnitrosamine and the amines which can form these nitrosamines (see Fig. 2).



**Figure 1**

**Figure 2:** Dimethylnitrosamine and dibutylnitrosamine

Like most N-nitrosamines, the substances to be assessed here are also genotoxic and carcinogenic in animal experiments. The N-nitrosamines are the most extensively processed group of substances in toxicology. In particular dimethyl- and diethylnitrosamine have been used as model substance in numerous studies. N-nitrosamines must be activated metabolically by cytochrome-P-450-monoxygenases whereby different isoenzymes are of

importance for the various substances. In the case of dimethyl and diethylnitrosamines this is CYP2E1-isoenzyme. The reactive intermediates formed react with DNA in the respective target organ by forming specific DNA adducts.

Several publications are also available on the nitrosatable precursors of N-nitrosamines. These are mainly aliphatic secondary amines that occur for instance in the gastrointestinal tract of experimental animals and humans. In the presence of nitrosating agents they can be converted into N-nitrosamines.

One characteristic of N-nitrosamines is the pronounced organ specificity of their carcinogenic effect which is influenced by various factors: chemical structure of the N-nitrosamine, species, type of application, dose, length of exposure. The preferred target organs of the substances to be assessed here - dimethylnitrosamine, diethylnitrosamine and dibutylnitrosamine - are the liver, kidneys, oesophagus, respiratory tract and bladder. As N-nitrosamines can induce tumours in almost all species (proven in more than 40 animal species), it can be assumed that they also have a carcinogenic effect in humans. A specific promutagenic DNA adduct (O<sup>6</sup>-methylguanine) was found in the human liver after fatal intoxication with dimethylnitrosamine; the same adduct was also found in human pancreatic cells after *in vitro* exposure. These experimental findings prove that human tissue is also capable of activating dimethylnitrosamine. Epidemiological indications of the carcinogenicity of N-nitrosamines in humans have been provided by studies in conjunction with the use of a specific chewing tobacco in the USA.

### 3.1.2 Exposure

We do not know of any findings from experiments seeking to determine exposure to N-nitrosamines from balloons. There are, however, results from migration experiments which can be used to estimate exposure.

Official tests of balloons in Rheinland-Pfalz and Mecklenburg-Vorpommern determined migratable levels of N-nitrosamines and nitrosatable portions using the method in BgVV Recommendation XXI (one-hour contact at 40 °C with the test solution). For dimethylnitrosamine migration levels were determined between 2 and 273 µg per kg consumer product; diethylnitrosamine was only detected in one case (2394 µg per kg) as was nitrosodibenzylamine (61 µg/kg). For nitrosodibutylamine the migration values were 21, 267 and 1845 µg/kg. In earlier tests from Baden-Württemberg, which had been submitted for assessment to BgVV, similar levels had also been identified (diethylnitrosamine: 434 and 449 µg/kg; dibutylnitrosamine 192 and 3084 µg/kg).

BgVV is of the opinion that a surface-related procedure is adequate for estimating exposure from balloons whereby 1 kg balloon would correspond to approximately 400 dm<sup>2</sup>. At a level of 400 µg diethylnitrosamine per kg balloon, it could be assumed that based on surface there would be 400 µg / 400 dm<sup>2</sup> (1 µg / dm<sup>2</sup>). If one assumes an exposure surface for a balloon of 10 cm<sup>2</sup> and, as the worst case scenario, that the entire N-nitrosamine content was ingested, this would lead to an intake of maximum 0.1 µg diethylnitrosamine. Although it is unlikely that the entire migratable content of a balloon would be taken up, several balloons are frequently involved.

By way of comparison the intake was estimated which could result under similarly unfavourable assumptions from a teat/soother of 10 g that complies with the provisions of the Consumer Products Ordinance. If one assumes a N-nitrosamine level of 10 µg/kg and also assumes that the entire N-Nitrosamine content was ingested, this would then lead to an intake of maximum 0.1 µg N-nitrosamine. From this exposure-related comparison it can be concluded that a balloon with a level of 400 µg/kg N-nitrosamine would not lead to any higher N-nitrosamine exposure than a teat/soother that complies with the requirements of the Consumer Products Ordinance. Far higher intake levels would result for a balloon for which a

level of 3084 µg/kg dibutyl nitrosamine had been measured. Using the exposure conditions outlined above this could theoretically lead to an intake of 0.8 µg.

When assessing N-nitrosamine exposures from toys of this kind, it is also important to know the exposure to N-nitrosamines is from other sources, e.g. food. For adults it was estimated from the consumption data of the Nutrition Report 1988 of the German Nutrition Society that the intake was between 0.2 (women) and 0.3 (men) µg N-nitrosamines per day. The main portion is attributed to dimethylnitrosamine; according to these information sources there is no dietary intake of diethyl- or dibutyl nitrosamine.

From the above data and estimations it can be concluded that the intake of N-nitrosamines from highly contaminated balloons under the most unfavourable circumstances could exceed dietary intake. However, this is not permanent intake as is the case with food; exposure is sporadic and the "worst case" has been used for the estimation.

### 3.1.3 Hazard potential

*Dimethylnitrosamine* (CAS-No. 62-75-9, N-nitrosodimethylamine, N,N-dimethylnitrosamine), *diethylnitrosamine* (CAS-No. 55-18-5, N-nitrosodiethylamine, N,N-diethylnitrosamine) and *dibutyl nitrosamine* (CAS-No. 924-16-3, N-nitrosodi-n-butylamine, N,N-Di-n-butyl nitrosamine) are classified as carcinogenic C2 according to chemical legislation (substances which are probably carcinogenic to humans). The substances belong to the group of particularly dangerous carcinogenic N-nitrosamines and, by extension, to the particularly dangerous carcinogenic hazardous substances to which workers may not be exposed pursuant to § 15a of the Hazardous Substances Ordinance. According to § 35 of the Hazardous Substances Ordinance preparations of  $\geq 0.0001$  % (1 ppm, 1 mg/kg) of this substance are to be considered carcinogenic. According to the Annex to § 1 Section 20 of the Chemical Ban Ordinance, preparations containing this concentration of N-nitrosamines may not be sold to private end users.

In accordance with Annex 4 to § 5 of the Consumer Products Ordinance no procedures may be used during the production of teats/soothers made of elastomer which lead to N-nitrosamines or substances which can convert to N-nitrosamines in a saliva solution being released from the teats/soothers in an amount that can be detected using the method described in Annex 10 No. 6. This means that the maximum level of migrated N-nitrosamines must be below 10 µg/kg rubber part and that the totality of all nitrosatable substances in the migrate may not exceed 100 µg/kg rubber part. According to BgVV Recommendation XXI Consumer products on the basis of natural or synthetic rubber, the guidance value of 10 µg/kg N-nitrosamines per kg consumer products must also comply with by consumer products in the special category that also includes balloons. There is a surface-related limit of 5 µg/dm<sup>2</sup> for the release of nitrosatable substances from balloons.

The dose-response studies on carcinogenic potential are of particular importance with regard to the carcinogenic risk from small doses. They have been conducted amongst other things with diethylnitrosamine in more than 4000 rats. The substances were administered in drinking water (BIBRA Study). These experiments established that, at low doses, there is a linear relationship between dose and carcinogenic effect and that there is no sign of a threshold dose. Based on the dose-response functions, for instance for a dose of 0.01 ppm corresponding to a body dose of approximately 0.5 µg per kg body weight and day, an additional risk of 0.25 % was calculated for the triggering of liver tumours in experimental animals. For dimethylnitrosamine the liver tumour risk in this study was established as  $0.8 \times 10^{-3}$  for 1 µg per kg body weight and day. These data do not constitute an incidence determined in experiments but are the result of a risk assessment. Of course, these numbers also only apply to the given trial test conditions (lifelong exposure) and the rat strain examined; it is not possible to directly transfer them to humans. There are no corresponding data for dibutyl nitrosamine.

### 3.1.4 Risk characterisation

The BIBRA Study examined, amongst other things, the influence of the rats' age at the start of exposure to diethylnitrosamine. There was found to be a far higher sensitivity (factor 6) to the hepatocarcinogenic effect of diethylnitrosamine when the animals were younger at the start of treatment. We must, therefore, assume a higher sensitivity for the group in the population which has a particularly high exposure to balloons – children – than for adults. According to the results of the combination tests in experimental animals, an additive carcinogenic effect must be expected for N-nitrosamines with a similar organotropism.

### 3.2 Assessment

The N-nitrosamines dimethylnitrosamine, diethylnitrosamine and dibutylnitrosamine are very similar in toxicological terms. From the wealth of available toxicological data it is estimated that they are genotoxic carcinogens. The substances are efficacious in almost all the animal species examined which means that one must assume that they are carcinogenic in humans, too. According to chemicals legislation they are classified as C2 (substances that are probably carcinogenic to humans). The substances belong to the group of particularly dangerous carcinogenic N-nitrosamines and, by extension, to the especially dangerous carcinogenic hazardous substances to which workers may not be exposed pursuant to § 15a of the Hazardous Substances Ordinance. According to § 35 of the Hazardous Substances Ordinance preparations of  $\geq 0.0001\%$  (1 ppm, 1 mg/kg) of these N-nitrosamines are deemed to be carcinogenic. According to the Annex to § 1 Section 20 of the Chemicals Ban Ordinance, preparations which contain this concentration of these N-nitrosamines may not be sold to private end users. We are of the opinion that the latter ban provision leads to a similar estimation for balloons that products which contain migratable portions of  $\geq 1$  mg/kg, should be equated with carcinogenic preparations and not sold to private end users either. This applies not only to the substances to be assessed here but also to the entire group of particularly dangerous carcinogenic N-nitrosamines.

In a exposure-related comparison it was established that a balloon with a content of 400 µg/kg N-nitrosamine did not lead to a higher N-nitrosamine exposure than a teat/soother that complies with the requirements of the Consumer Products Ordinance. Far higher intake levels would result for a balloon for which a level of 3084 µg/kg dibutylnitrosamine had been measured. Using the exposure conditions outlined and assumed above this would lead to a theoretical intake of 0.8 µg. This would exceed the dietary intake of N-nitrosamines. However this is not permanent intake as is the case for foods; exposure is sporadic and the worst case has been used for this estimation. When it comes to a possible carcinogenic effect, children must be deemed to be an especially sensitive risk group; furthermore N-nitrosamines must be assumed to have an additive effect. A propensity to damage health cannot, therefore, be ruled out.

According to Annex II of the Directive concerning the safety of toys, one of the main safety requirements for toys is that they must be safe in terms of their chemical characteristics. No levels of dangerous substances or preparations may be contained in toys within the intendment of Directives 67/548/EEC and 88/379/EEC that could prove harmful for children when they play with the toy. We are of the opinion that all cases in which the value of 400 µg/kg was exceeded constitute a clear violation of these requirements and, by extension a violation of the Ordinance on the safety of toys. For precautionary purposes efforts should be made to remain below the guidance value of 10 µg/kg in Recommendation XXI.

In this context an opinion is expressed on the question about how to assess cases in which the maximum levels or guidance levels in BgVV recommendations are exceeded with regard to § 30 Foods and Other Consumer Products Act (LMBG). The BgVV recommendations are shaped by the precautionary principle. Through the values established there the tolerable daily intakes derived from toxicological studies are not normally exhausted. It is far more the

case that the principle is pursued of keeping consumer exposure to a minimum in accordance with the technological state of the art. In the case of compliance with the BgVV recommendations it can be assumed that consumer products are safe. If these requirements are not complied with – for instance, maximum levels, guidance levels or migration values are exceeded - then this does not simply mean that the conclusion can be drawn that the consumer products are harmful within the intendment of § 30 LMBG. For assessments of this kind concrete exposure to the substance in the corresponding consumer product must be estimated and a toxicological risk assessment undertaken. In addition to the above considerations it should generally be required that, in the case of genotoxic carcinogens for which as a rule no threshold value can be given, exposure should be minimised in accordance with the technological state of the art. For the N-nitrosamines this means that the demand for compliance with Recommendation XXI should be upheld.

### 3.3 Measures

The levels of N-nitrosamines in balloons discussed here are avoidable according to the technological state of the art; hence the resulting N-nitrosamine exposures are unacceptable. In terms of precautionary consumer health protection it is frequently very difficult to refer to § 30 LMBG. It is, therefore, suggested that the Consumer Products Ordinance should be amended along the lines that not only teats/soothers but also balloons and other consumer products in the special category of Recommendation XXI be covered by the ban in § 5 of the Ordinance.

This topic has also been discussed by the BgVV Plastics Committee. It expressly indicated its support for the above proposal. In particular the representatives of the regional public agencies point to the need for legally binding rules for the release of N-nitrosamines and substances which can be converted to N-nitrosamines for toys made of rubber as the legal provisions which apply to toys have not taken this problem into account up to now. The studies in conjunction with the official monitoring of consumer products repeatedly identified very high release values particularly for balloons. There is no sign of a solution to this problem on the European level. In the standardisation project "Safety of Toys - Organic Chemical Compounds" N-nitrosamines and nitrosatable substances are not included in the mandate of the European Commission. The following regulatory proposal resulted from the deliberations of the BgVV Plastics Committee.

*The guidance values of Recommendation XXI for the release of N-nitrosamines and N-nitrosatable substances for toys and balloons made of natural and synthetic rubber are taken over into the Consumer Products Ordinance, i.e. 0.01 mg N-nitrosamines and 0.1 mg N-nitrosatable substances per kg elastomer. By way of deviation from this, the release of N-nitrosatable substances from balloons should be restricted in terms of surface to 0.005 mg/dm<sup>2</sup>. The test is carried out after 1-hour contact at 40 °C with the saliva test solution in accordance with Annex 10 No. 6 to the Consumer Products Ordinance.*

From the technological angle there has been a shift in recent years to the use of vulcanisation accelerators from which less dangerous N-nitrosamines like dibenzyl nitrosamine are formed during rubber production. At the workplace there is a call for the use of less dangerous substitutes (TRGS 552). For instance the employment ban in § 15a of the Hazardous Substances Ordinance only applies to specific N-nitrosamines like dimethylnitrosamine, diethylnitrosamine and dibutylnitrosamine; the less dangerous N-nitrosamines (e.g. dibenzyl nitrosamine) are exempt from this ban. It is proposed that industry should be encouraged to use less dangerous vulcanisation accelerators during the production of consumer products in accordance with TRGS 552. If this proves viable, then it would be possible to amend the Consumer Products Ordinance in such a way that only the use of "safe" amines would be allowed which means that no carcinogenic N-nitrosamines would be formed. This requires an amendment to Commission Directive 93/11/EEC of 15 March 1993 concerning the release of the N-nitrosamines and N-nitrosatable substances

from elastomer or rubber teats and soothers. This would constitute major progress in the efforts of consumer health protection to reduce consumer exposure, particularly the exposure of children to carcinogenic substances.

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