



Nitrosamines

Carcinogenic process contaminants

Initial products in the formation of N-nitrosamines are nitrosating substances such as nitrite and nitrosatable amines found in many areas of the human environment. Nitrosamines are present, for example, in food, tobacco, cosmetics and consumer goods made of latex. Medicines can also contain nitrosamines as impurities. Most N-nitrosamines are regarded as genotoxic, and carcinogenic in animal studies.

Chronology of thematic focal points

In the 1980s, Switzerland introduced a stringent limiting value of 0.5 µg/kg for volatile nitrosamines in beer. The focus is on the nitrosamine NDMA which can form during the curing of malt. To comply with the limiting value for beer, NDMA values in malt should not exceed 2 µg/kg. Earlier, beer and malt coffee contained large amounts of nitrosamines. Technical modifications in the production of malt have now made it possible to greatly reduce concentrations. In addition to tobacco smoke, the main sources of nitrosamine today include spices, cured meats and smoked bacon, to which nitrite curing salt is added for the purpose of reddening and preservation. However, not all of these products generally contain nitrosamines.

Nitrosamine formation is also possible in the human organism itself («endogenous» contamination), because the environment as well as food contain nitrosatable amines and nitrosating substances. After transition from the product into human saliva or gastric juice, these substances can change into carcinogenic nitrosamines. Of interest in the case of products containing nitrosatable amines is the potential for nitrosamine formation which serves as a measure of the corresponding endogenous contamination. Accordingly, for example, the nitrosation potential of medicines with secondary amino groups is examined in the scope of regulatory approvals.

Nitrosatable amines from elastomer or rubber parts are also endogenous sources; appropriate limits on their quantity are therefore imposed on bottle teats and soothers for infants and young children. In addition to NDMA in foodstuffs and animal feed, the most frequent requests for determination address the release of nitrosamines and nitrosatable substances from elastomers and rubber of bottle teats and soothers (refer to DIN EN 12868) as well as balloons.

Analysis of nitrosamines in water is also of increasing importance due to the upgrading of wastewater treatment plants with the additional cleaning stage of ozonization.

Examination of nitrosamines in medicines and their raw materials is currently at the focus. Several hypotensive medicines containing the active ingredient Valsartan were recently recalled because individual batches were contaminated with the potentially carcinogenic N-nitrosodimethylamine (NDMA). Global research has led to detection of nitrosamine contamination in further medicines, such as NDMA in Ranitidine or NMBA in Losartan.



Nitrosamine analysis at Labor Veritas AG

Labor Veritas AG has a long tradition of determining of nitrosamines. The employed analytical methods of measurement have proven themselves for a diversity of samples. Routinely examined N-nitrosamines are listed in Table 1.

Name	Abbreviation	CAS number	Measurement methods (primary)	(alternative)
N-Nitrosodibutylamine	NDBA	924-16-3	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosodiethylamine	NDEA	55-18-5	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosodiisopropylamine	NDIPA	601-77-4	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosodimethylamine	NDMA	62-75-9	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosodipropylamine	NDPA	621-64-7	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosoethylisopropylamine	NEIPA	16339-04-1	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosomethylethylamine	NMEA	10595-95-6	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosomorpholine	NMOR	59-89-2	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosopiperidine	NPIP	100-75-4	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitrosopyrrolidine	NPYR	930-55-2	GC-TEA, GC-MS/MS	LC-APCI-MS/MS
N-Nitroso-N-methylaniline	NMPhA	614-00-6	GC-MS/MS ¹	LC-ESI-MS/MS ¹
N-Nitroso-N-ethylaniline	NEPhA	612-64-6	GC-MS/MS ¹	LC-ESI-MS/MS ¹
N-Nitroso-N-methyl-4-aminobutyric acid	NMBA	61445-55-4	LC-APCI-MS/MS	GC-MS/MS ¹
N-Nitroso-N-methyl-4-aminobutyric acid methylester	NMBAMe	51938-17-1	LC-APCI-MS/MS	GC-MS/MS
N-Nitroso-N-methyl-4-aminopropionic acid	NMPA	10478-42-9	LC-APCI-MS/MS	GC-MS/MS ¹
N-Nitroso-N-methyl-aminopropionic acid methylester	NMPAMe	383417-47-8	LC-APCI-MS/MS	GC-MS/MS
Nitrosobis(2-hydroxyethyl)amine	NDELA	1116-54-7	LC-APCI-MS/MS	GC-MS/MS ¹

Table 1: Nitrosamines examined at Labor Veritas AG (¹ feasibility checked but not yet integrated into validated methods)

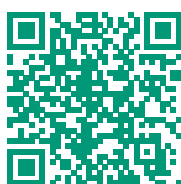
Volatile nitrosamines in food, consumer goods and water samples are usually analyzed by means of GC-TEA, or alternatively GC-MS/MS. Analysis using LC-APCI-MS/MS has proven itself for less volatile nitrosamines, especially pharmaceutical products and raw materials.

Sample shipment

Samples can be shipped by regular mail. For cross-border shipping, a green customs slip CN22 must be affixed to the package, and its contents must be declared as samples of goods. The sample quantities listed in Table 2 are required to achieve the specified determination limits.

Sample material	Determination limit	Required sample quantity
NDMA in malt	0.8 µg/kg	300g
NDMA in seasoning and beer	0.2 µg/kg	100ml
NDMA in feed	2 µg/kg	300g
NDMA in baby milk powder	2 µg/kg	100g
N-nitrosamines in water (individual substances)	10 ng/l	1 l
N-nitrosamines in bottle teats and soothers (total)	10 µg/kg	30 g
N-nitrosatable substances in bottle teats and soothers (total)	100 µg/kg	30 g
N-nitrosamines in pharmaceutical products and raw materials	5–30 µg/kg	10 g

Table 2: Determination limits and sample quantities



Contact persons



Service catalogue

Scan & Go: Download QR-code reader from the App Store (iOS) or Play Store (Android), scan a code, and discover more.

Labor Veritas AG, Postfach, CH-8027 Zürich
Phone: 044 283 29 30, Fax: 044 201 42 49
admin@laborveritas.ch, www.laborveritas.ch