RISK MITIGATION OF NITROSAMINES FORMATION IN DRUG PRODUCTS:

Role of Excipients

Ricarda Leister – Head of R&D

MEGGLE Excipients, Wasserburg, Germany

1. Introduction

The issue of Nitrosamine impurities in drug and excipient manufacturing has become a significant concern for the pharmaceutical industry and health authorities. In June 2018, the FDA was notified of the presence of N-nitrosodimethylamine (NDMA), an impurity found in valsartan, an angiotensin II receptor blocker. In July EMA issued a press-release regarding the recall of some Valsartan medicines following the detection of an impurity. Then, several other medications, including Ranitidine, Nizatidine, and Metformin, have been found to contain unacceptable amounts of Nitrosamines.

The term Nitrosamine describes a class of compounds having the chemical structure of a nitroso group bonded to an amine (R1N(-R2)-N=O). The compounds can be formed by a nitrosating reaction between amines and nitrous acid (nitrite salts under acidic conditions). Secondary amines are of greatest concern. However, tertiary amines can also undergo nitrosation via more complex pathways. All secondary and tertiary aliphatic and aromatic amines should therefore be considered, including those present as part of the starting material, intermediate or final structure as well as those introduced as reagents, catalysts, solvents or as impurities. The reaction can be catalysed by heat and acidic conditions.

Some Nitrosamines are classified as probable or possible human carcinogens by the International Agency for Research on Cancer (IARC). They are referred to as „cohort of concern" compounds in the ICH guidance for industry M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. The guidance recommends that any known mutagenic carcinogen, such as nitroso compounds, should be controlled at or below levels such that there is a negligible human cancer risk associated with exposure to potentially mutagenic impurities.

Several authorities issued guidance (EMA, FDA) and information on Nitrosamine impurities and requested Marketing Authorization Holders (MAHs) to conduct a risk evaluation with regards to Nitrosamine formation in their drug products.

Excipients may contribute to the formation of Nitrosamines through precursor substances present in the excipient (e.g. nitrites, amines). Nitrite impurities are found in most of the commonly used excipients, at least in traces. A recent publication by Boetzel et al. (2022) has reported the nitrite values of commonly used excipients, referencing a database established by Lhasa Limited. However, the original manufacturer names are not disclosed. Furthermore important to note is that the values were measured or provided by different companies within the consortium, and the analytical methods used were not standardized. Therefore, it cannot be ruled out that some of the observed variability may be attributed to the analytical methods employed.

2. Lactose: Level of Nitrite and Potential Sources

Lactose has typically a very low nitrite content. In the publication from Boetzel et al. (2022) the nitrite content for Lactose from eight suppliers ranged from 0.07 to 1.7 ppm, with a mean of 0.54 ppm (table 1). Microcrystalline Cellulose showed a similar range from 0.04 to 2.4 ppm, with a mean of 0.70 ppm. Whereas Crospovidone had the highest levels with a mean of 8.3 ppm and a maximum value of 14 ppm nitrite.

Table 1. Nitrite Results of Eight Selected Excipients in the Database and the Number of Excipient Suppliers the Excipients were Sourced from. (Boetzel et al., 2022)

Excipients	Nitrite Results (µg/g)				No. of Suppliers	No. of Results
	Min	Mean	Median	Max		
Corn starch	0.055	0.21	0.15	0.61	6	20
Croscarmellose sodium	0.17	0.42	0.33	1.0	4	14
Crospovidone	0.79	6.5	8.3	14	5	15
Hypromellose	0.01	0.80	1	5.0	5	49
Lactose Monohydrate	**0.07**	**0.54**	**0.5**	**1.7**	**8**	**34**
Magnesium stearate	0.1	2.6	2.4	6.1	9	44
Microcrystalline cellulose	0.04	0.70	0.5	2.4	9	73
Povidone	0.10	0.83	0.5	2.3	5	52

However, as the nitrite contribution is assumed as additive the sum and total amount of all excipients in the formulation have to be considered. As fillers/diluents are typically used in larger proportions they could play an important role even if their nitrite content is comparably low.

There seems to be some confusion in the ongoing discussions regarding the presence of nitrite in excipients (USP Nitrosamine Exchange). On the one hand there is a lot of uncertainty regarding the potential origin of the nitrite. On the other hand, there is a misconception regarding the term „nitrite-free," which is not an absolute definition, but rather dependent on the sensitivity of the analytical method or the applied limits. For example, a product can be labelled „non-alcoholic" in the United States and the European Union if it contains no more than 0.5 % alcohol by volume. The key question is what limits for nitrite are appropriate.

Scientifically derived limits for nitrite levels should be set for critical active ingredients, bearing in mind that „nitrite-free" excipients may not be achievable. This is simply a matter of method sensitivity (detection limit). Water and other natural materials (plant-based or animal-based) contain at least traces of nitrite.

One of the main sources of nitrate and nitrite is the use of nitrogen-based fertilisers such as ammonium nitrate, urea and ammonium sulfate, which are commonly used to provide crops with the necessary nutrients for growth. Following the biochemical reactions of the nitrogen cycle ammonium is converted to nitrite (NO_2^-), this is called nitrification. Nitrification is a two-step aerobic biological process that involves the oxidation of ammonium to nitrite, and then further oxidation of nitrite to nitrate (NO_3^-). Bacteria responsible for these conversions are called nitrifying bacteria and are typically present in soil, water, and wastewater in various species and strains.

Another source of nitrite in water is acid rain. When nitrogen oxides, specifically nitrogen dioxide (NO_2) and nitric oxide (NO) are released into the atmosphere as air pollutants. These dissolve in rainwater and form nitric acid (HNO_3). Nitric acid can further react with other compounds in the environment and eventually convert to nitrite (NO_2^-) in water. Nitrogen oxides (NOx) originate from reactions of nitrogen as component of the air with oxygen at high temperatures, typically above 1,000 degrees Celsius, e.g. during combustion.

3. Nitrites in MEGGLE Excipients

We have been monitoring nitrite content of Lactose regularly since many years. As nitrate content is also important for baby food, we have implemented a method, specifically designed for milk products, and that is sensitive enough to determine low nitrite content as required for infant milk products (ISO 14673-3:2007-05). For our pharma grade Lactose it has been found that nitrite is typically not detectable in the Lactose powder (below detection limit of 0.2 ppm), or at least below the quantification limit of 0.5 ppm (table 2). Notably all values are lower than the mean reported for Lactose by Boetzel et al. (2022). Further information and discussion regarding the analytical method to determine nitrite in excipients is given in chapter 4.

Lactose is a natural material and not chemically synthesized. Organic solvents, catalysts and other reagents which might be a reason for the presence of secondary, tertiary or quaternary amines and nitrite salts are not used. The manufacturing of pharma grade Lactose includes several washing and raffination steps as well as a double crystallization. The manufacturing process does not create the highly acidic conditions necessary for the formation of Nitrosamines and for drying only indirect heating is used. There is no potential NOx generation from combustion.

On the other hand, Lactose monohydrate is isolated and purified from whey which is a by-product of cheese manufacturing. Therefore, nitrite traces might come from the raw material whey and water.

Testing on nitrates and nitrites is conducted as part of incoming goods inspection of the whey. The acceptance limits are as follows: Nitrate < 50 ppm, Nitrite < 5 ppm. The process water is regularly monitored according German TrinkwV and showed very low levels below 0.02 ppm over the past three years.

Table 2. Nitrites levels in MEGGLE Excipients, measured according ISO 14673-3:2007-05 by accredited laboratory. Limit of quantification (LOQ) 0.5 ppm, limit of detection (LOD) 0.2 ppm.

Brand name	Product category	Year	Nitrite [ppm]
Lactose Monitoring		2017-2022	Not detected; < 0.5 ppm
GranuLac® 200	milled Lactose	2022	Not detected
FlowLac® 100	spray-dried Lactose	2022	Not detected
Tablettose® 80	agglomerated Lactose	2022	< 0.5 ppm
CelLactose® 80	co-processed: Lactose + cellulose powder	2022	Not detected
MicroceLac® 100	co-processed: Lactose + MCC	2022	Not detected
StarLac®	co-processed: Lactose + starch	2022	< 0.5 ppm
CombiLac®	co-processed: Lactose + MCC + starch	2022	< 0.5 ppm

Relevant factors, as well as measured values, can be found in the supplier statement along with the IPEC Questionnaire for the respective materials.

The IPEC Federation recently provided an updated „Questionnaire for Excipient Nitrosamines Risk Evaluation" (Feb 2023). This questionnaire reflects considerations for excipients from the guidance from the EMA, including the „Questions and answers for marketing authorization holders" and the FDA Guidance for Industry „Control of Nitrosamine Impurities in Human Drugs". The questionnaire includes a matrix to consider the structure and the origin of the excipient as a first indication of risk, as well as measured values for nitrite and Nitrosamines. The use of a standard format facilitates the collection of data from excipient suppliers and assists pharmaceutical manufacturers in their Nitrosamine risk assessment.

It should be noted that the excipient manufacturer cannot carry out a Nitrosamine risk assessment as this requires specific knowledge of the actual drug formulation and the properties of the active substance.

4. Strategies for Mitigating Risks in Drug Product Manufacturing

As first step the risk of Nitrosamine formation or impurities in APIs has to be assessed. The recent publication from Nanda et al. "Inhibition of N-Nitrosamine Formation in Drug Products investigating possible APIs and formation mechanisms" (2021) provides valuable insights.

The EMA requires Marketing Authorization Holders (MHA) to perform the following risk assessment steps:

Step 1: MAHs to perform a risk evaluation to identify if APIs and/or Finished Products could be at risk of presence of Nitrosamine

Step 2: If a risk is identified: MAHs has to proceed with confirmatory testing in order to confirm or refute the presence of Nitrosamines.

Step 3: If the presence of Nitrosamine(s) is confirmed:, MAHs should implement effective risk mitigating measures through submission of variation.

When a (potential) risk of Nitrosamine formation has been identified, the best risk mitigation strategies have to be evaluated. Besides the API manufacturing process and possible adaptions thereof, the formulation and used excipients as well as the drug product manufacturing process should be reviewed and if needed variations filed. A detailed description and points to consider can be found in the Q&A from EMA, in the following paragraph we highlight only aspects regarding excipients and drug product manufacturing process.

To mitigate the risk the following potential formulation and process changes might be applied:

- Conducting testing of batches from various suppliers to evaluate differences in nitrite content and considering a supplier change, in case of significant differences in nitrite content.
- Consider exchanging an excipient with another excipient type that has the same functionality but lower nitrite values (e.g. disintegrant).
- Reduce the amount, relative to the API, of excipients with high nitrite content.
- Explore other formulation strategies, such as adding suitable antioxidants, pH modifiers or nitrite scavengers.
- Avoid process conditions that promote Nitrosamine formation during drug manufacturing, especially water and heat. Use direct compression instead.
- Avoid water uptake by using excipients with low water activity, such as Lactose monohydrate or using packaging with improved water vapor barrier.
- Ensure that packaging lidding foils do not contain Nitrocellulose.

Changing the excipient manufacturer, is with regards to the regulatory requirements, the easiest option for existing products. In case of unexpected high values or differences it is advisable to get in direct contact with supplier.

In a study regarding N-nitrosodimethylamine formation in metformin (Schlingemann et al., 2022), a significant difference between API manufacturing sites as well as between excipient suppliers has been identified.

Potential inhibitors, include for example Ascorbic acid, Sodium ascorbate, α-Tocopherol, Caffeic acid and Ferulic acid as well as Amino acids (Glycine, Lysine, Histidine) as scavengers (Nanda et al., 2021; Bayne et al., 2023).

In case of issues with marketed products also a formulation changes to a direct compression formulation might be a good option. The addition of water to the drug product process, increases the risk of N-Nitrosamine formation during processing and growth upon storage. Moser et al. (2023) demonstrated in a recently published study that direct compression reduces the risk of N-Nitrosamine formation compared to wet granulation in systems with similar materials.

MEGGLE´s product range offers a selection of different excipients designed to support direct compression processes. In our Innovation & Formulation Campus we can assist with trials regarding a potential reformulation.

5. Analytical Method for Nitrite Determination

As the nitrite content of excipients at trace levels play an important role a few considerations regarding the analytical method should be done.

There have been significant advances in providing a sensitive standard method to determine Nitrosamines in ppb level. However, there is not yet an established standard method for determining nitrite levels in excipients at trace levels. Boetzel et al. (2022, Lhase Nitrite database) reported that as analytical technique for the determination of the nitrite content Ion chromatography with conductivity detection has been used mostly (67 %, with different sample preparation techniques). Further 29 % of the results have been obtained by using Griess reaction in combination with liquid chromatography and UV-Vis detection. The remaining few analysis used either UV/Vis spectroscopy with Gries reaction (2 %) or only UV-Vis spectroscopy (2 %).

The Griess reaction is a well-established method commonly used for detecting nitrites in different samples. This method is based on the selective reaction of nitrite with sulfanilic acid and N-(1-naphthyl) ethylenediamine dihydrochloride under acidic conditions, resulting in a red-violet azo dye that can be measured using spectrophotometry. By comparing the absorbance values of a sample at 540nm to a predetermined standard curve, the concentration of nitrite in the sample can be calculated.

For nitrite and nitrate determination in dairy products ISO norms are available (milk and milk product - Determination of nitrate and nitrite contents, ISO 14673-1, -2 and -3). The methods are based on spectrometric detection after Griess reaction.

Method 2 uses segmented flow analysis (SFA) and method 3 flow injection analysis (FIA). Nitrate can be determined with these methods after cadmium reduction of nitrate to nitrite. MEGGLE uses method ISO 14673-3:2007-05 for routine monitoring of Lactose products.

This consists of an automatised flow-injection analysis with in-line dialysis as pretreatment and spectroscopic detection of the red azo dye (Griess reaction) at 540 nm. This method is designed to fulfill also the strict baby food requirements (milk powder and milk-based infant food). Limit of quantification (LOQ) is 0.5 ppm and the limit of detection (LOD) is 0.2 ppm.

For water and environmental testing, ion chromatography with conductivity and UV/VIS detection has become the standard method for determining different anions simultaneously, including nitrite (e.g. ISO 10304-1:200-07). Ion chromatography bases on the exchange and separation of ions depending on their charge and affinity towards the applied stationary phase (ion exchange column). The separated ions are then detected and quantified using conductivity measurement or UV/VIS spectroscopy. However, one of the main challenges of ion chromatography is its susceptibility to interference from the product matrix (matrix effect), which may contain ions that can interfere with the separation and quantification of the target ions, leading to inaccurate results, as well as co-elution.

For example, the presence of organic acids such as Lactic acid, Acetic acid, and Citric acid in the matrix can affect the separation and UV/VIS detection at the typically used low wavelength for nitrite (210 nm). Similarly, the presence of anions like chloride can interfere with conductivity measurements, and cations like Sodium, Potassium, and Calcium or Proteins in the matrix can also worsen the separation or overload the column. To minimize these matrix effects, sample preparation techniques such as in-line dialysis, precipitation or filtration/pre-columns may be used. Selective ion exchange resins and eluents can aid in the separation of the target ions from the interferences in the matrix (Gapper et al., 200; Jireš, J. & Douša, M., 2022, Thermo Scientific Application Note 279).

Gapper et al. (2004) reported a high-performance ion-exchange methods incorporating on-line post-column reduction with either cadmium or vanadium, coupled to derivatization with Griess reagent and detection at 540 nm, for dairy products and baby foods. This chromatographic separation of nitrate and nitrite, combined with specific post-column conversion to the chromophoric azo derivative, avoids the potential matrix interference limitations of conventional assays and the inherent disadvantages of other reported chromatographic detection modes.

High pressure ion exchange coupled with mass spectrometry (Ngere et al., 2023) or UHPLC with MS (Jireš, J. & Douša, M., 2022), could be an alternative reference method to overcome interference challenges. Nevertheless, these methods are often costly and less practical as a routine testing method.

Other promising trace methods have been comprehensively reviewed by Moorcroft et al. (2001) and Wan et al. (2017). However, the methods compared in their reviews were mostly used for nitrite determination of water/wastewater or biological fluid matrices.
Finally, it is crucial to validate the method for each type of matrix to ensure accurate and reliable results.

6. Summary & Outlook

In order to minimize the risk of N-Nitrosamine formation in drug products, careful selection of API and excipients in terms of type and amount is crucial. The API manufacturing process and potential impurities or precursors have to be considered primarily. However, also the drug product manufacturing process itself can impact the formation of Nitrosamines. Direct compression is the preferred process as it avoids the use of water and heat. Existing formulations can usually be reformulated accordingly.

MEGGLEs specially designed excipients for direct compression can help you to switch from wet-granulation to direct compression, reduce amount of excipients in the formulation, reduce required compression pressure or decrease the amount of disintegrant needed, thus mitigating the risk of N-Nitrosamine formation.

The Nitrosamine risk statement with the IPEC questionnaire can be used as a starting point for excipient selection. In frame of the supplier selection and qualification for critical products, nitrite of different suppliers and batches should be tested. However, it is important to note that the analytical method used to determine the nitrite content should be carefully reviewed regarding potential matrix interferences. Moreover, pre-tests on actual blends are advisable, as not all solid-state interactions driving N-nitrosamine formation in solid dosage formulations are fully understood yet. Further research is needed to uncover other factors that may affect solid-state reactions, such as local pH gradients, presence of reactive functional groups, counter-ion effects, morphological forms, particle size and surface area of the constituents.

Scientifically derived limits for nitrite levels should be established for critical APIs, keeping in mind that excipients „free" of nitrite may not be achievable. It is simply a question of the method sensitivity (detection limit). Additional testing and purification steps may come at additional costs. Moreover, the establishment of a standard method for nitrite testing in excipients would be highly recommended to ensure comparable and meaningful values to support customers in the excipient selection and evaluation process.

If you would like to learn more about how MEGGLE can help you mitigate the risk associated with Nitrosamines, please contact us.

References

Bayne v. A.C., Misic Z., Stemmler R.T., Wittner M., Frerichs M., Bird J.K., Besheer A. (2023). N-Nitrosamine mitigation with nitrite scavengers in oral pharmaceutical drug products. Journal of Pharmaceutical Sciences https://doi.org/10.1016/j.xphs.2023.03.022

Boetzel, R., Schlingemann, J., Hickert, S., Korn, C., Kocks, G., Luck, B., Blom, G., Harrison, M., François, M., Allain, L. R., Wu, Y. & Bousraf, Y. (2022). A Nitrite Excipient Database: A useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products. Journal of Pharmaceutical Sciences. https://doi.org/10.1016/j.xphs.2022.04.016

DIN EN ISO 10304-1:2009-07, Wasserbeschaffenheit_- Bestimmung von gelösten Anionen mittels Flüssigkeits-Ionenchromatographie_- Teil_1: Bestimmung von Bromid, Chlorid, Fluorid, Nitrat, Nitrit, Phosphat und Sulfat (ISO_10304-1:2007); Deutsche Fassung EN_ISO_10304-1:2009. (2019). Beuth Verlag. https://doi.org/10.31030/1518948

DIN EN ISO 14673-1:2004-05, Milch und Milchprodukte_- Bestimmung des Nitrat- und Nitritgehaltes_- Teil_1: Verfahren mit Cadmiumreduktion und Spektrometrie (ISO_14673-1:2004); Deutsche Fassung EN_ISO_14673-1:2004. (2019). Beuth Verlag. https://doi.org/10.31030/9540983

DIN EN ISO 14673-2:2004-05, Milch und Milchprodukte_- Bestimmung des Nitrat- und Nitritgehaltes_- Teil_2: Verfahren mit segmentierter Fließanalyse (Routineverfahren) (ISO_14673-2:2004); Deutsche Fassung EN_ISO_14673-2:2004. (2019). Beuth Verlag. https://doi.org/10.31030/9540984

DIN EN ISO 14673-3:2004-05, Milch und Milchprodukte_- Bestimmung des Nitrat- und Nitritgehaltes_- Teil_3: Verfahren mit Cadmiumreduktion und Fließinjektionsanalyse mit In-line-Dialyse (Routineverfahren) (ISO_14673-3:2004); Deutsche Fassung EN_ISO_14673-3:2004.(2019). Beuth Verlag. https://doi.org/10.31030/9540985

EMA. Nitrosamine impurities - European Medicines Agency. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/Nitrosamine-impurities#guidance-for-marketing-authorisation-holders-section

EMA.Q&A :Questions and answers for marketing authorization holders/applicants on CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on Nitrosamine impurities in human medicinal products EMA/CHMP/409815/2020 Rev. 11. 29 July 2022.

EMA ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Scientific guideline European Medicines Agency. European Medicines Agency. https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential

Excipients | Lhasa Limited. Lhasa Limited. https://www.lhasalimited.org/initiatives/nitrites.htm
FDA ResearchControl of Nitrosamine Impurities in Human Drugs. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-Nitrosamine-impurities-human-drugs

Fritzsche, M., Blom, G., Keitel, J., Goettsche, A., Seegel, M., Leicht, S., Guessregen, B., Hickert, S., Reifenberg, P., Cimelli, A., Baranowski, R., Desmartin, E., Barrau, E., Harrison, M., Bristow, T., O'Neill, N., Kirsch, A., Krueger, P., Saal, C., . . . Schlingemann, J. (2022). NDMA analytics in metformin products: Comparison of methods and pitfalls. European Journal of Pharmaceutical Sciences, 168, 106026. https://doi.org/10.1016/j.ejps.2021.106026

Gapper, L. W., Fong, B., Otter, D., Indyk, H. E. & Woollard, D. C. (2004). Determination of nitrite and nitrate in dairy products by ion exchange LC with spectrophotometric detection. International Dairy Journal, 14(10), 881–887. https://doi.org/10.1016/j.idairyj.2004.02.015#

IPEC Questionnaire for Excipient Nitrosamines Risk Evaluation, Feb 2023. https://www.ipec-europe.org/articles/questionnaire-for-excipient-Nitrosamines-risk-evaluation.html

Jireš, J. & Douša, M. (2022). Nitrites as precursors of N-nitrosation in pharmaceutical samples – A trace level analysis. Journal of Pharmaceutical and Biomedical Analysis, 213, 114677. https://doi.org/10.1016/j.jpba.2022.114677

Moorcroft, M. J., Davis, J. & Compton, R. G. (2001). Detection and determination of nitrate and nitrite: a review. Talanta, 54(5), 785–803. https://doi.org/10.1016/s0039-9140(01)00323-x

Moser, J., Ashworth, I. W., Harris, L., Hillier, M. C., Nanda, K. K. & Scrivens, G. (2023). N-Nitrosamine Formation in Pharmaceutical Solid Drug Products: Experimental Observations. Journal of Pharmaceutical Sciences. https://doi.org/10.1016/j.xphs.2023.01.027

Nanda, K. K., Tignor, S., Clancy, J. W., Marota, M., Allain, L. R. & D'Addio, S. M. (2021). Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study. Journal of Pharmaceutical Sciences, 110(12), 3773–3775. https://doi.org/10.1016/j.xphs.2021.08.010

Ngere, J. B., Ebrahimi, K. H., Williams, R., Pires, E., Walsby-Tickle, J. & McCullagh, J. S. O. (2023). Ion-Exchange Chromatography Coupled to Mass Spectrometry in Life Science, Environmental, and Medical Research. Analytical Chemistry, 95(1), 152–166. https://doi.org/10.1021/acs.analchem.2c04298

Schlingemann, J., Boucley, C., Hickert, S., Bourasseau, L., Walker, M. L., Celdran, C., Chemarin, T., Pegues, C., Fritzsche, M., Keitel, J., Goettsche, A., Seegel, M., Leicht, S., Guessregen, B., Reifenberg, P., Wetzel, S. J., Müller, T. O., Schooren, F., Schuster, T., . . . Masanes, S. (2022). Avoiding N-nitrosodimethylamine formation in metformin pharmaceuticals by limiting dimethylamine and nitrite. International Journal of Pharmaceutics, 620, 121740. https://doi.org/10.1016/j.ijpharm.2022.121740

Thermo Scientific, Application Note 279, Time Savings and Improved Reproducibility of Nitrate and Nitrite Ion Chromatography Determination in Milk Samples | SelectScience. SelectScience. https://www.selectscience.net/application-notes/time-savings-and-improved-reproducibility-of-nitrate-and-nitrite-ion-chromatography-determination-in-milk-samples/?artID=23548"

USP Nitrosamines Exchange: Nitrosamines Exchange: A knowledge based community for all-things Nitrosamine. https://Nitrosamines.usp.org/

Wang, Q., Yu, L., Liu, Y., Lin, L. P., Lu, R., Zhu, J., He, L. & Lu, Z. (2017). Methods for the detection and determination of nitrite and nitrate: A review. Talanta, 165, 709–720. https://doi.org/10.1016/j.talanta.2016.12.044

Wherever you are – we are there for you.

Do you have sales related questions?
Our field sales representatives are available worldwide:

Africa and Middle East
T +20 100 1486 826
hani.calache@meggle.com

Asian Regions
T +65 9232 3378
siangmeng.chua@meggle.sg

China
T +86 21 3393 2457 308
yi.kang@meggle-china.com

Japan
T +81 3 3561 3491
yokomizo@meggle.co.jp

Europe
T +49 8071 73 118
info.excipients@meggle.com

USA and Canada
T +1 845 289 0264
customer.service@meggle.com

Central and South American Regions
T +55 11 2893 4831
fabio.ikuno@meggle.com

Do you need technical support?
Our experts in excipients are there for you worldwide.
Please contact

Technical department
T +49 8071 73 623

Research and Development
T +49 8071 73 812

www.meggle-excipients.com

MEGGLE GmbH & Co. KG - Business Unit Excipients