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Mitigating Nitrosamine Impurities in Pharmaceuticals: A Comprehensive Review

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Abstract:

Nitrosamines, a class of substances recognised for their high mutagenic potency and classified as probable human carcinogens, have raised significant concerns within the pharmaceutical industry and regulatory authorities. These impurities may originate from reagents, catalysts, solvents, or raw materials used in manufacturing processes and may contaminate drug substances and products. The presence of nitrosamine impurities in various medications, including valsartan, tetrazole-containing angiotensin II receptor blockers, ranitidine, metformin, and other pharmaceutical products, has led to numerous recalls and shortages. Beyond their carcinogenic risks, nitrosamines are implicated in the development of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, as well as type-2 diabetes. Consequently, effective mitigation strategies, including advanced analytical techniques such as LC-MS, GC-MS, CE-MS, and SFC, are essential for controlling or avoiding these impurities. Regulatory authorities, such as the USFDA, EMA, ICH, and WHO, play a critical role in addressing the risks associated with nitrosamine contamination. They should continue to provide guidance and periodic updates to drug manufacturers and applicants to ensure compliance and risk mitigation. Concurrently, manufacturers are encouraged to exercise diligence in preventing the occurrence of nitrosating agents and secondary amines during production processes. By implementing analytical methodologies that are both practical and compliant with industry requirements, and by addressing existing gaps in impurity detection, the pharmaceutical industry can significantly enhance the framework for nitrosamine risk evaluation, thereby reducing their adverse effects on public health.

Keywords: nitrosating agents, nitrosamine impurity, hydrazide, amines, sartan, genotoxic, carcinogenicity.

Introduction

Nitrosamines represent a class of compounds that have been recognized since the 19th century(Akkaraju, H.; Tatia, R.; Mane, S. S.; Khade, A. B.; Dengale)(*Witt, O. N. XXIII.□On Aromatic Nitrosamines. J. Chem. Soc. 1878, 33, 202−211*). Their utilization in organic chemistry has remained relatively restricted, primarily serving as solvents or synthetic intermediates(*Magee, P. N.; Barnes, J. M. The Production of Malignant Primary Hepatic*

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Tumours in the Rat by Feeding Dimethylnitrosamine. Br. J. Cancer 1956, 10 (1), 114)(*VRZAL, T.; OLSOVSKA, J. N-Nitrosamines in 21th Century. Kvasny Prumysl 2016, 62 (1), 2−8VRZAL, T.; OLSOVSKA, J. N-Nitrosamines in 21th Century. Kvasny Prumysl 2016, 62 (1), 2−8*). However, an exception to this limited application is N-nitrosodimethylamine (NDMA), which has been produced on an industrial scale for the synthesis of 1,1-dimethylhydrazine(Manchuri et al.).

They are characterized by the presence of the nitroso functional group. These compounds are commonly found in various environmental and consumer sources including water, food, tobacco, pesticides, and plastics. Public awareness of nitrosamines significantly increased in mid-2018, following their detection in pharmaceutical products (*World Health Organization (WHO). Information Note Nitrosamine Impurities [Displayed 24 September 2020]. Available at Https://Www.Who.Int/Medicines/Publications/ Drugalerts/InformationNote_Nitrosamine-Impurities/En/*).

Table 1: Sources of Nitrosating agent

Amine sources	Nitrosating agents	
2^0 amines	Nitrous acid	
3^0 amines	Nitrile in acidic condition	
Cyanamide	Nitrosyl chloride	
Guanamide	Nitrous oxide	
Amidines	Nitrosonium	➡ **Nitrosamines**
Hydroxylmines	Tetrafluoroborate	
Hyadrazines	And Nitric Oxide/Oxygen	
Hydrazones		
Hydrazides		

Among these, N-nitrosamines are recognized as highly potent mutagenic carcinogens and have been classified as a “cohort of concern” by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH guideline focuses on the assessment and control of DNA-reactive (mutagenic) impurities in pharmaceuticals to mitigate potential carcinogenic risk(*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Guideline M7(R1) on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk [Displ*).

The most prominent examples within this class, N-nitroso-dimethylamine (NDMA) and N-nitroso-diethylamine (NDEA), have been categorised by the International Agency for Research on Cancer (IARC) as probable human carcinogens (Group 2A). Additionally, these compounds

exhibit genotoxic properties (*European Medicines Agency (EMA). Lessons Learnt from Presence of N-Nitrosamine Impurities in Sartan Medicines [Displayed 24 September 2020]. Available at Https://Www. Ema.Europa.Eu/En/Documents/Report/Lessons-Learnt-Presence n-Nitrosamine-Impurities-Sarta*).

As of 2022, animal studies involving 228 low molecular weight nitrosamine derivatives revealed that 82% of these compounds are considered in-vivo carcinogens, irrespective of the route of administration (Dobo KL, KenyonMO, Dirat O)(Thresher A, Foster R, Ponting DJ, Stalford SA, Tennant RE).

Nitrosamines generally necessitate metabolic activation to initiate carcinogenesis. According to the widely accepted mechanism, nitrosamines undergo α-hydroxylation mediated by cytochrome P450 enzymes, resulting in the formation of reactive intermediates such as diazonium ions or carbocations, which subsequently interact with DNA to cause mutagenic effects (Brambilla G, Mattioli F, Robbiano L).

The α-hydroxy-N-nitrosamines, highly reactive intermediates, exhibit significant instability in vitro under aqueous conditions at physiological pH, with half-lives measured in seconds. Notably, these intermediates are also formed in vivo as part of the biochemical pathways by which nitrosamines interact with DNA, contributing to their carcinogenic effects(Li Y; Preussmann R; H.; R.; Brambilla G, Mattioli F, Robbiano L).

Nitrosamines exhibit a range of synthetic transformations, demonstrating their versatility in chemical reactivity. These compounds can undergo protonation in acidic solutions, predominantly at the oxygen atom, enabling them to function as Lewis bases and hydrogen bond acceptors. Under acidic conditions, de-nitrosation, the reverse process of nitrosation, may occur either in the absence or presence of catalytic nucleophiles like bromide, yielding secondary amines and nitrous acid.

Nitrosamines are also amenable to reduction under various conditions, such as catalytic hydrogenation or conversion into hydrazine derivatives through dissolving metal and hydride reductions. Their oxidation via peroxide reagents is a common method employed for synthesising N-nitramines. Furthermore, photolytic rearrangement of nitrosamines can produce the corresponding amidoximes.

N-Nitrosamines can be formed from amines and nitrosating agents (generally oxidised nitrogen-containing compounds, NOx) under certain reaction conditions. Nitrous acid forms salts with basic amines which, when heated, can further react to afford N-nitrosamines. These NOx species have different reactivities and can react with amines differently depending on, for example, the pH of reaction medium and the nature of the solvent. At low pH, more powerful nitrosating reagents are present, but the amine is protonated and thus, less reactive. Therefore, effective nitrosating conditions in aqueous solution depend on the nitrosating species, the pH and the basicity of the amine, having optimum formation rates at low pH (Horne et al.).

Table 2: Examples of nitrosamine precursors- nitrosating agents

Potential sources of nitrosating agents	Examples
Synthetic reagents	Nitrous acid, sodium nitrite, nitroalkanes or alkyl nitrites
Contaminants in reagents and solvents	Nitrite in sodium azide, nitrate salts
By-products	Nitric acid under reducing conditions, hydroxylamines under oxidising conditions, nitromethane rearrangement to methyl nitrite
Processing aids	Activated charcoal catalysed the fixation of nitrogen gas from air and the formation of reactive nitrogen agents
Impurities in water	Chloramine,nitrite
Unit operations	NO from air and heating during fluid bed drying

ICH classification of Nitrosamines:

Nitrosamine impurities are classified as Class 1 under the ICH M7 (R1) guidelines, owing to their established mutagenic and carcinogenic properties based on rodent carcinogenicity and mutagenicity data. These impurities disrupt genetic material through mechanisms such as chromosomal breaks, rearrangements, covalent bonding, or incorporation into DNA during replication, [EMA]. This classification emphasizes the necessity for stringent controls to mitigate the risks associated with these substances in pharmaceuticals.

Sources of Nitrosamine Impurities

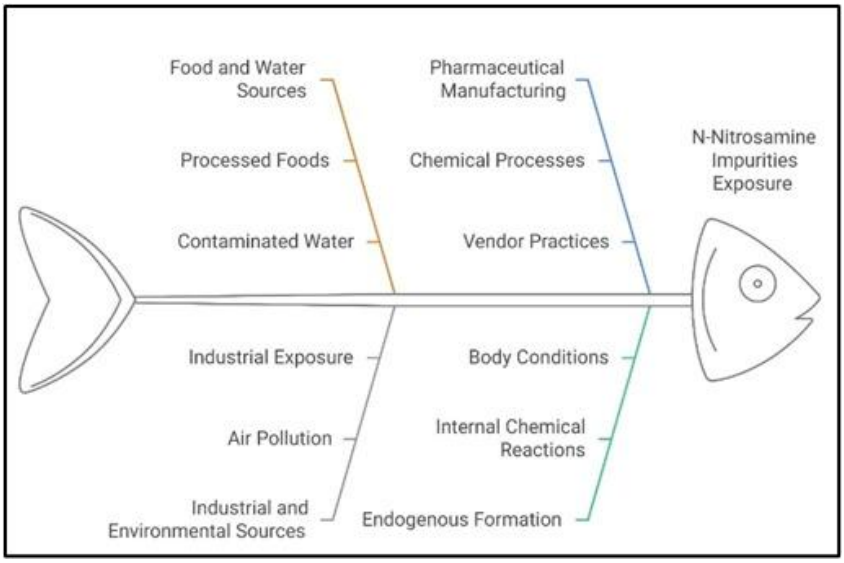


Figure 1: Fishbone diagram of sources of nitrosamine impurities

Table 3: Amines and corresponding Nitrosamine impurities.

Amines	Corresponding Nitrosamine impurities
Dimethylamine	N-nitrosodimethylamine (NDMA)
Diethylamine	N-nitrosodiethylamine (NDEA)
Dipropylamine	N-nitrosodipropylamine (NDPA)
Diisopropylamine	N-nitrosodiisopropylamine (NDIPA)
Dibutylamine	N-nitrosodibutylamine (NDBA)
Ethylmethylamine	N-nitrosomethylethylamine (NMEA)
4-(methylamino)butanoic acid	N-nitroso-N-methyl-4-aminobutyric acid (NMBA)

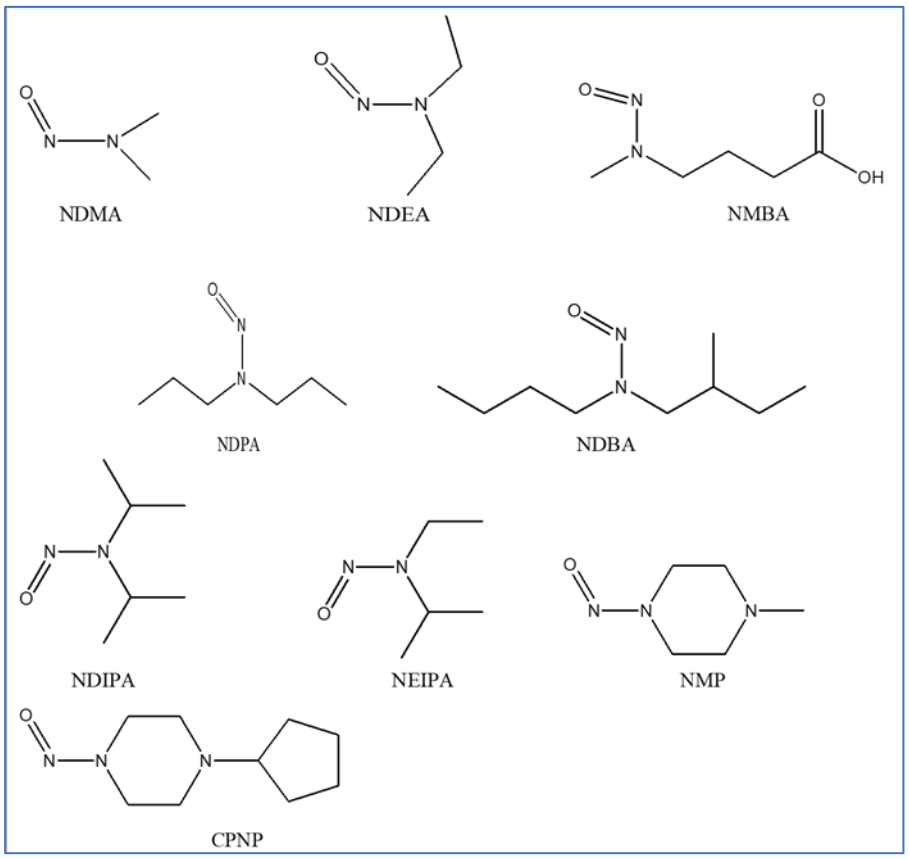


Figure 2: Chemical structures of the medicines with nitrosamine issues and various nitrosamine impurities reportedly identified in pharmaceuticals.

Formation of Nitrosamine impurity

The reaction pathway demonstrates the nitrosation of dimethylamine by sodium nitrite under acidic conditions, leading to the formation of N-nitroso-dimethylamine. This transformation exemplifies the vulnerability of secondary amines to nitrosamine generation, a process of significant toxicological concern. NDMA formed through this route is relatively stable, though

minor decomposition may occur, contributing to its persistence in pharmaceutical and environmental systems. Such mechanistic insight underscores the importance of controlling nitrite levels and amine precursors during drug synthesis to prevent nitrosamine contamination.

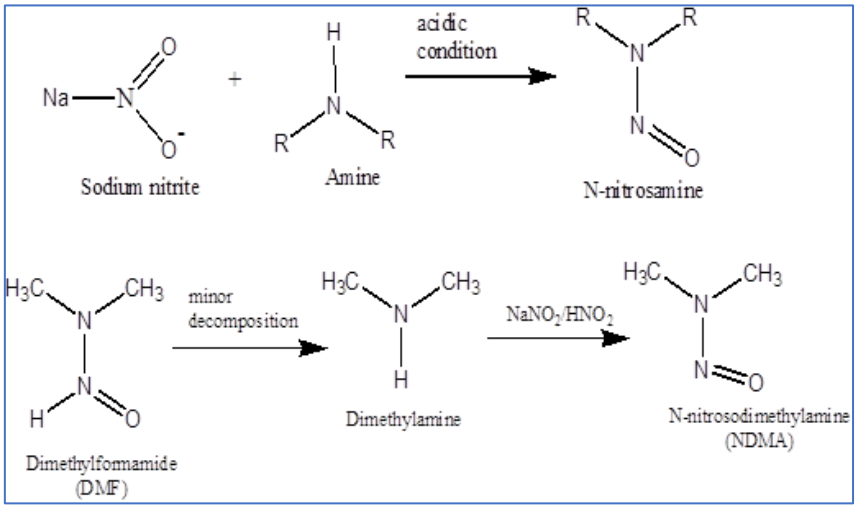


Figure 3: Formation of Nitrosamine impurity, eg, NDMA

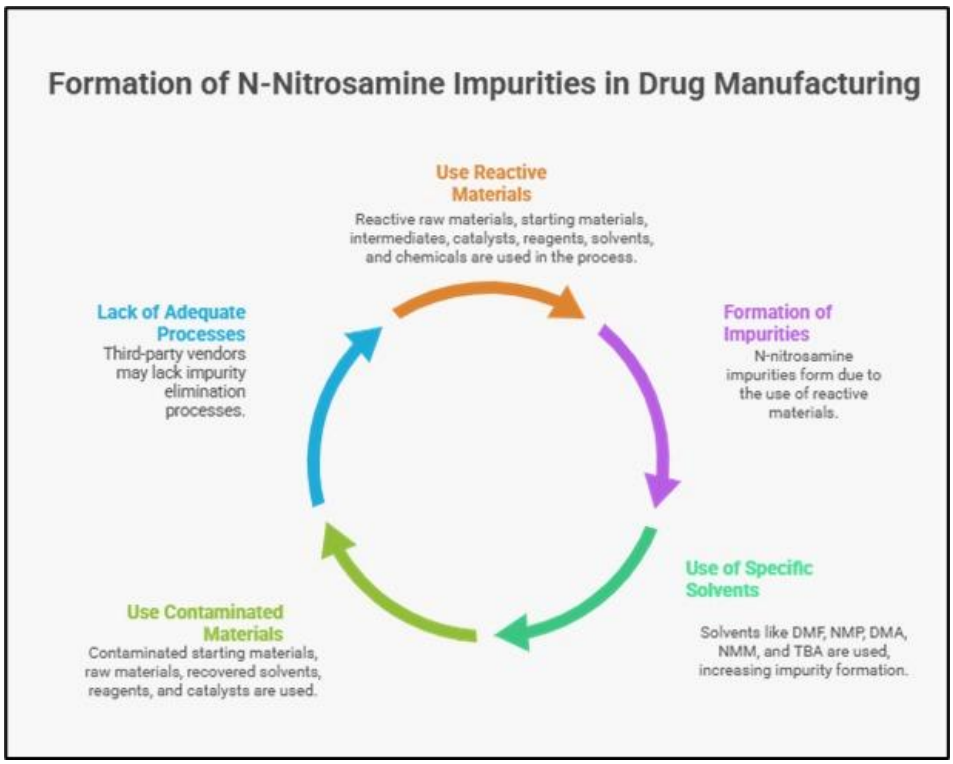


Figure 4: Formation of N-nitrosamine impurities in drug manufacturing

Mechanism of Nitrosamine Impurity Formation

The nitrosation of secondary amines in alkaline environments proceeds via a carboxylate-mediated pathway, wherein proton transfer equilibria sustain the regeneration of nitrosamine species. This mechanistic framework emphasizes the persistence of nitrosative chemistry beyond acidic matrices, underscoring its relevance to pharmaceutical stability, excipient compatibility, and long-term safety evaluation in drug formulations.

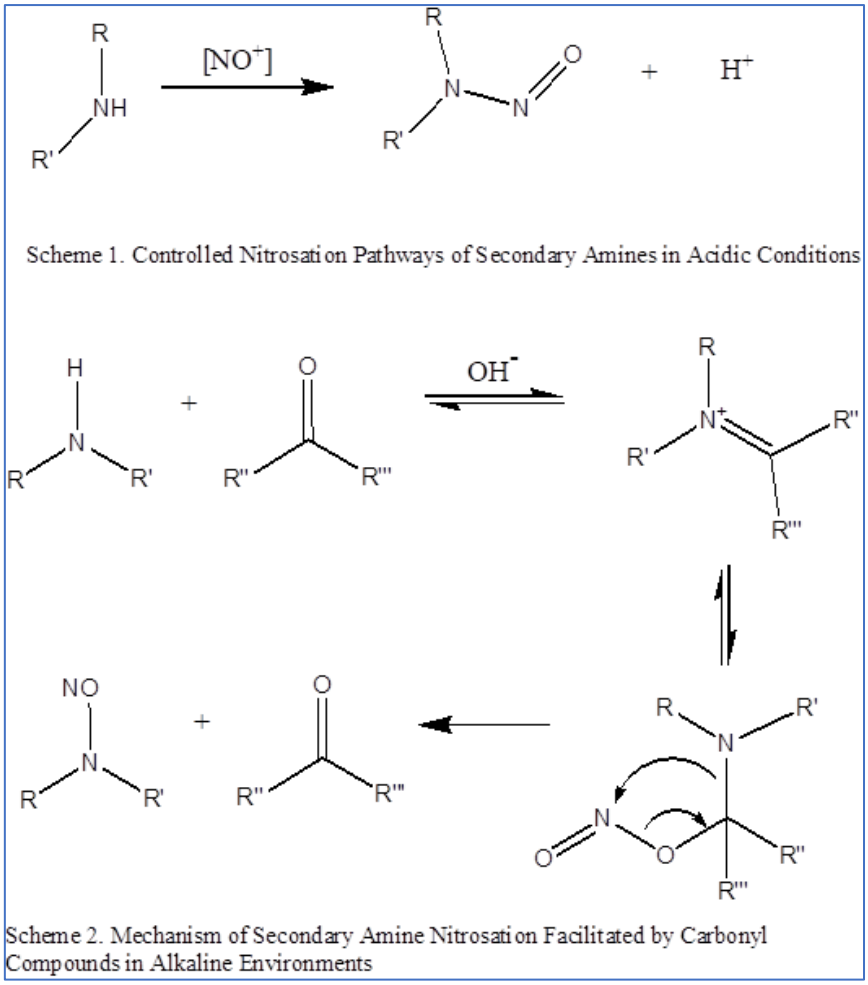


Figure 5: Source of Nitrosamine Contamination in Pharmaceuticals **[3]**

Available software programs to predict or confirm n-nitrosamine impurities

Available software programs to predict or confirm N-nitrosamine impurities In the pharmaceutical and personal care sectors, quantum mechanical and chemical methodologies are commonly employed to predict the carcinogenic potential and DNA reactivity of N-nitroso impurities. This approach, referred to as computer-aided discovery and redesign (CADRE), has gained prominence (*Kostal, J.; Voutchkova-Kostal, A. Quantum-Mechanical Approach to Predicting the Carcinogenic Potency of N-Nitroso Impurities in Pharmaceuticals. Chem. Res. Toxicol. 2023, 36 (2), 291−304.*)(*Wenzel, J.; Schmidt, F.; Blumrich, M.; Amberg, A.; Czich, A. Predicting DNA-Reactivity of N-Nitrosamines: A Quantum Chemical Approach. Chem. Res. Toxicol. 2022, 35 (11), 2068−2084*). Additionally, a web-based automated SMILES-based screening application has been developed to evaluate the risk category of N-nitrosamine compounds based on their SMILES notation, enabling rapid screening to identify high-risk N-nitrosamine formations (*Zhu, J.; Qu, Y.; Ye, N. An Automated Carcinogenic Potency Categorization Approach for Nitrosamine Drug Substance-Related Impurities †. Green Chem. 2024, 26, 3717*).

In silico risk assessment techniques are increasingly applied to evaluate the likelihood of N-nitrosamine formation and other mutagenic impurities during API production. The U.S. FDA

has introduced a structural similarity-based approach to identify surrogate compounds for carcinogenicity assessment. Beyond predictive modeling, several analytical software platforms are widely used to confirm nitrosamine impurities in drug substances and products, including Thermo Fisher Scientific Solutions (LC-MS/MS, HRAM spectrometry), Waters waters_connect™ Software, and the Agilent Nitrosamine Impurities Application Guide. These advances highlight the growing reliance on computational and analytical tools to enhance pharmaceutical safety and efficacy(*Murphy, N. S.; O'connor, D. C.; Gavins, G. C.; James, L.; Lockett, J. P.; Mcmanus, J. A.; Packer, G.; Lopez-Rodríguez, R.; Webb, S. J.; Burns, M. J. Identifying the Risk of Formation of Nitrosamines and Other Potentially Mutagenic Impurities during API Ma*)(*Kruhlak, N. L.; Chakravarti, S.; Kumaran, G.; Saiakhov, R. A for Assessing the Carcinogenicity of Nitrosamine Impurities. FDA, 2022.*).

Analytical techniques for detection of Nitrosamines

The National Institutes of Health (NIH) has established and validated an innovative analytical method for detecting four specific N-nitrosamine impurities - NDMA, NDEA, NMBA, and NEIPA - in pharmaceutical formulations of valsartan, losartan, and irbesartan. This methodology employs high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS), utilising atmospheric pressure chemical ionization (APCI) as the ionization source. (*Khorolskiy, M.; Ramenskaya, G.; Vlasov, A.; Perederyaev, O.; Maslennikova, N. Development and Validation of Four Nitrosamine Impurities Determination Method in Medicines of Valsartan, Losartan, and Irbesartan with HPLC-MS/MS (APCI). Iranian Journal of Pha*).

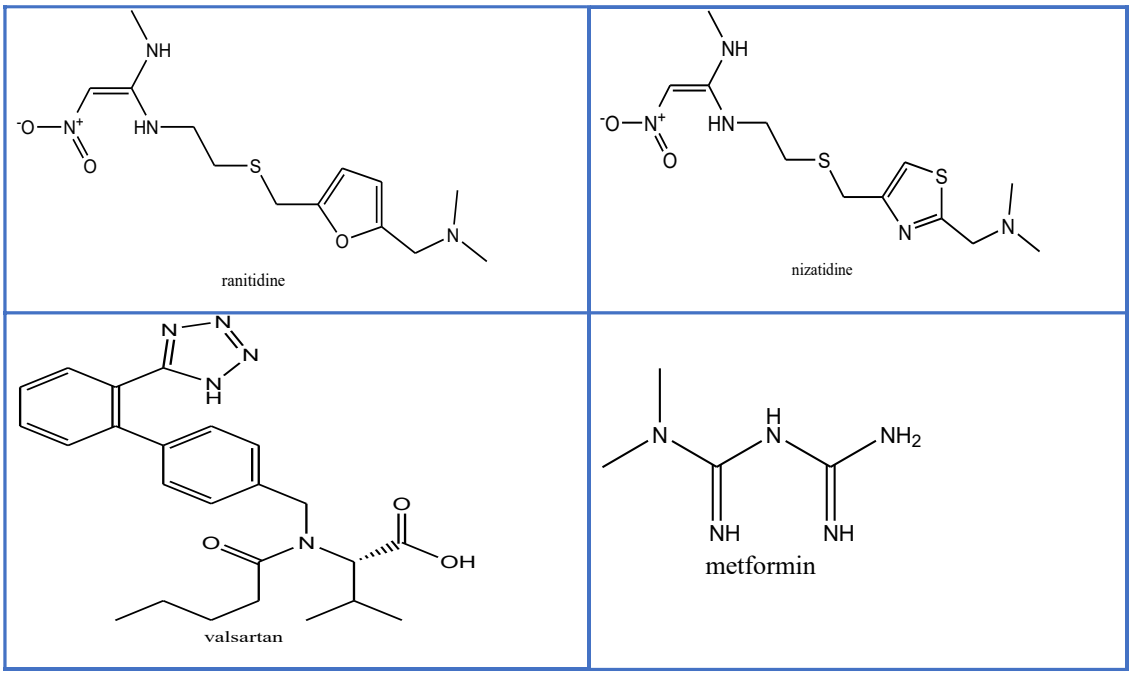
Furthermore, numerous HPLC-based techniques have been developed and reported by researchers for the quantification of various N-nitrosamine impurities across multiple drug formulations. These include atorvastatin, itraconazole (Takahashi et al.), diovan, losartan(*Analysis of Nitrosamines Using Unique Stationary Phase Technology- Feb 01 2022- Joseph J. Pesek, Maria T. Matyska, Tanya Hiltz- Life Science News Articles- Labmate Online. Https://Www. Labmate-Online.Com/Article/Chromatography/1/Microsolv Technology-Corp/*), enalapril maleate (*Boczar, D.; Wyszomirska, E.; Zabrzewska, B.; Chyła, A.; Michalska, K. Development and Validation of a Method for the Semi Quantitative Determination of n-Nitrosamines in Active Pharmaceut Ical Ingredient Enalapril Maleate by Means of Derivatisation and De*), propranolol (*Partani, P.; Choudhary, S.; Bharataiya, P.; Gunta, U.; Kumar Ponnamaneni, R.; Pillai, M.; Baghla, R.; Nandita, E. Sensitive and ReproducibleQuantificationofN-NitrosoPropranololinaPropranolol Drug Substance and Product Featuring a Workflow for Quantifying*), valsartan (*Masada, S.; Tsuji, G.; Arai, R.; Uchiyama, N.; Demizu, Y.; Tsutsumi, T.; Abe, Y.; Akiyama, H.; Hakamatsuka, T.; Izutsu, K. Ichi; Goda, Y.; Okuda, H. Rapid and Efficient High-Performance Liquid Chromatography Analysis of N-Nitrosodimethylamine Impurity In*), and lisinopril (*Tsanaktsidou, E.; Kanata, L.; Almpani, S.; Zacharis, C. K.; Markopoulou, C. K. Development and Validation of an HPLC-FLD Method for the Determination of NDMA and NDEA Nitrosamines in Lisinopril Using Pre-Column Denitrosation and Derivatization Procedure.*). These advancements underscore the significance of employing sensitive and robust analytical approaches to ensure

the detection and quantification of potentially harmful N-nitrosamine impurities in pharmaceutical products, thereby safeguarding public health.

In addition to pharmaceutical applications, high-performance liquid chromatography methods have been developed and reported for the detection and quantification of N-nitrosamine impurities in diverse matrices, including water (*Lee, M.; Lee, Y.; Soltermann, F.; Von Gunten, U. Analysis of N Nitrosamines and Other Nitro(so) Compounds in Water by High Performance Liquid Chromatography with Post-Column UV Photol Ysis/Griess Reaction. Water Research 2013, 47, 4893.*), cigarettes (*Wang, A.-J. An Abstract of the Thesis of Title HPLC Analysis and Reactions of N-Nitrosamines. 1987*), and food products (*Ding, Z.; Cai, M.; Gan, W.; Yuan, P.; Wei, L.; Cheng, X. Analytical Methods Studies on a Novel Method for the Determination of Nitrosamines in Food by HPLC-UV-FLD Coupling with Terbium Doped Carbon Dots. Food Chem. 2023, 405, 134894.*).

Furthermore, several LC-MS techniques have been extensively developed and documented by researchers for the analysis of N-nitrosamine impurities in various drug formulations. Examples include ranitidine, utilizing a bioanalytical method (*DePalma,R.;Patel, V.; Florian, J.; Keire, D.; Selaya, D.; Strauss, D. G.; Rouse, R.; Matta, M. K. A Bioanalytical Method for Quantification of N-Nitrosodimethylamine (NDMA) in Human Plasma and Urine with Different Meals and Following Administration of Ran*); losartan (*Yang, J.; Kakarla, R.; Marzan, T.; Sherwin, B.; George, M.; Bennett, J.; Basutto, J.; Su, Y.; Ollerenshaw, J.; Morin, J.; Rebi Ere, H.; Maggio, A.-F.; Kermaïdic, A.; Gervela, E.; Brenier, C.; Civade, C.; Chauvey, D.; Duperray, F.; Wollein, U.; Conti, M.;*); ranitidine (*Rao, G. S.; Ramadevi, D.; Rao, B. M.; Rajana, N.; Basavaiah, K. Novel Stability Indicating LC-MS Method for N-Nitroso Dimethyl Amine Genotoxic Impurity Quantification in Ranitidine Drug Substance and Drug Product ARTICLE INFO. J. Appl. Pharm. Sci. 2022, 1*); rifampicin (*De Souza, G. F. P.; Araujo Vieira Matos, M. F.; de Castro Aglio, T.; Salles, A. G.; Rath, S. A Comprehensive LC-UHPLC-MS/MS Method for the Monitoring of N-Nitrosamines in Lipophilic Drugs: A Case Study with Rifampicin. J. Pharm. Biomed Anal 2023, 236, 115*);telmisartan(*Chidella, K. S.; Dasari, V. B.; Anireddy, J.; Chidella, K. S.; Dasari, V. B.; Anireddy, J. Ultra-Sensitive LC-MS/MS Method for the Trace Level Quantification of Six Potential Genotoxic Nitrosamine Impurities in Telmisartan. Am. J. Analyt Chem. 2021, 12 (6*); azilsartan, telmisartan and irbesartan(*Reddy Gopireddy, R.; Maruthapillai, A.; Tamilselvi, M. Determination of Potential Nitrosamines NDMA, NDIPA and N Nitroso Duloxetine in Duloxetine Hydrochloride ByLC-MS/MSUsing APCI Source. Materials Today: Proceedings 2022, 68, A7*); duloxetine(*Reddy Gopireddy, R.; Maruthapillai, A.; Tamilselvi, M. Determination of Potential Nitrosamines NDMA, NDIPA and N Nitroso Duloxetine in Duloxetine Hydrochloride ByLC-MS/MSUsing APCI Source. Materials Today: Proceedings 2022, 68, A7*); irbesartan (*Mavis, M. E.; Goksu Gursu, G.; Ular Cagatay, N. Development of a Sensitive LC-APCI-MS/MS Method for Simultaneous Determi Nation of Eleven Nitrosamines in Valsartan and Irbesartan with a Simple Extraction Approach. Journal of Chromatography B 2023, 1216, 1*); olmesartan(*González, R.; Torrado, G.; Arribas, J. M.; Pena, M. A. Development of an Analytical Method for the Determination and Quantification of N-Nitrosodimethylamine in Olmesartan by HPLC MS/MS. Microchemical Journal 2022, 179, 107402. .*); rifampicin(*Tao, X.; Tian, Y.; Liu, W. H.; Yao, S.; Yin, L. Trace Level Quantification of 4-Methyl-1-Nitrosopiperazin in Rifampicin Capsules*

by LC-MS/MS. Front Chem. 2022, 10, DOI: 10.3389/ Fchem.2022.834124); metformin(*Dharani, S.; Mohamed, E. M.; Khuroo, T.; Ali, H. I.; Reddy, I. K.; Rahman, Z.; Khan, M. A. In-Use Stability Assessment of FDA Approved Metformin Immediate Release and Extended Release Products for N-Nitrosodimethylamine and Dissolution Quality Attributes.*)(*Hao, G.; Hu,R.;Wang,X.;Gao,P.; Wang,L.;Jiang, M.; Xin, L.; Tan, G.; Zhao, Y.; Sun, F.; Chu, D.; Lv, J.; You, J.; Huang, F.; Song, X. N-Nitrosodimethylamine Formation in Metformin Hydrochloride Sustained-Release Tablets: Effects of Metformin and Hypromello*); valsartan (*Bodiwala, K. B.; Panchal, B. G.; Savale, S. S.; Dave, J. B.; Sureja, D. K.; Dhameliya, T. M.; Chhabria, M. T. Simultaneous Estimation of Six NitrosamineImpuritiesinValsartanUsingLiquidChromatographic Method. J. AOAC Int. 2022, 105, DOI: 10.1093/Jaoacint/Q*); rivaroxaban (*Kumar Baksam, V.; Saritha, N.; Rao Devineni, S.; Jain, M.; Kumar, P.; Shandilya, S.; Kumar, P. A Critical N-Nitrosamine Impurity of Anticoagulant Drug, Rivaroxaban: Synthesis, Characterization, Development of LC-MS/MS Method for Nanogram Level Quantifi Ca*).



These advancements highlight the broad applicability of chromatographic methods in ensuring the effective detection and quantification of N-nitrosamine impurities across multiple drugs and environmental sources, contributing significantly to public health and safety.

LC-MS methods have also been developed and reported for the quantification of N-nitrosamine impurities in various matrices, including cigarette tobacco, cigar tobacco, and smokeless tobacco (*Wu, J. Analysis of Tobacco-Specific Nitrosamines in Cigarette Tobacco, Cigar Tobacco, and Smokeless Tobacco by Isotope Dilution LC-MS/MS LCGC North America; 2020*), as well as tobacco and mainstream cigarette smoke (*Li, Y.; Pang, T.; Shi, J.; Liu, X.; Xu, Z.; Song, Z.; Xie, H. Determination of Tobacco-Specific Nitrosamines in Tobacco and Mainstream Cigarette Smoke Using One-Step Clean-up Coupled with Liquid Chromatography-Tandem Mass Spectrometry. J. Chromatogr A 202*). These methods have been further applied to analyze tobacco-specific N-nitrosamine impurities (*Lee, Y.-S.; Kim, K.-*

H.; Lee, S. S.; Brown, R. J. C.; Jo, S.-H. Analytical Method for Measurement of Tobacco-Specific Nitrosamines in E-Cigarette Liquid and Aerosol. Applied Sciences 2018, 8, 2699.), biopharmaceuticals (*Xie, Y.; Zhang, L.; Hou, W.; Cheng, Y.; Luo, F.; Liu, Z.; Zhang, Z. Pharmaceutical Biotechnology A Novel Method for Monitoring N Nitrosamines Impurities Using NH 2-MIL-101(Fe) Mediated Dispersive Micro-Solid Phase Extraction Coupled with LC-MS/MS in Bioph*), groundwater(*Chen, S.; Zhang, Y.; Zhao, Q.; Liu, Y.; Wang, Y.; Chen, S.; Zhang, Y.; Zhao, Q.; Liu, Y.; Wang, Y. Simultaneous Determination for Nine Kinds of N-Nitrosamines Compounds in Groundwater by Ultra High-Performance Liquid Chromatography Coupled with Triple Qua*), and wastewater (*Tang, H.; Li, Z.; Chen, H.; Xu, Y.; Jiang, X.; Du, E.; Lyu, Z.; Zheng, L.; Peng, M. An Online-SPE/SEC/LCMS Method for the Detection of N-Nitrosamine Disinfection Byproducts in Wastewater Plant Tailwater. Water 2022, Vol. 14, Page 2371 2022, 14 (15), 2371*). These advancements underline the versatility of LC-MS techniques in detecting and quantifying N-nitrosamine impurities across a diverse range of substances and environments.

During analysis, both in situ generation of nitrosamines and their contamination from reagents, e.g., water, must be prevented. As stated in the U.S. FDA's letter to Valisure LLC(*U.S. Food & Drug Administration. 2020. Final Response Letter from FDA CDER to Valisure, LLC. Letter. Available at: Https://Www.Regulations.Gov/Document?D=FDA 2019-P-4281-0008. Accessed May 12, 2020.*) Unsuitable test methods can cause artifactual levels of NDMA found in ranitidine. Analytical methods that can detect diverse nitrosamine species will be an asset to tackle any risks associated with the synthetic routes. Then, if toxicity data of the detected nitrosamines is not available, the toxicity levels for their mutagenicity and carcinogenicity can be characterized and used to assign their acceptable limits(Tuesuwan and Vongsutilers).

Table 4: Analytical methods for detection of nitrosamine(*The European Directorate for the Quality of Medicines & HealthCare (EDQM). 2019. LC-MS/MS Method for LOSARTAN Potassium. Test Method. Available at: Https:// Www.Edqm.Eu/Sites/Default/Files/De_lgl_losartan_method_parameters_nm Ba_lcms.Pdf. Accessed Decembe*)(*U.S. Food & Drug Administration. 2019. Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Raniti Dine Drug Substance and Drug Product. Test Method. Available at: Https://Www. Fda.Gov/Media/130801/Down*)(*The United State Pharmacopeia. 2020. <1469> Nitrosamine Impurities. General Chapter Prospectus. Available at: Https://Www.Uspnf.Com/Notices/Nitrosamine Impurities-Gc-Prospectus-20200424. Accessed December 1, 2020.*)

Sr. No.	Analytical method for detection of nitrosamine
1.	LC-MS/MS
2.	GC-MS
3.	LC-MS
4.	LC-HRMS(QTRAP)

5.	Headspace-SPME-GC−MS method
6.	SPE GC-MS/MS
7.	LC HRMS (QTRAP with APCI+)
8.	GC/MS

Limits and Acceptable intake

Nitrosamine impurities are classified as Class 1 according to the ICH guidelines due to their established carcinogenicity and mutagenicity. The acceptable intake (AI) for these mutagenic and carcinogenic impurities is determined using the median toxic dose (TD50), which represents the dose causing toxicity in 50% of cases. The ICH M7 (R1) guideline recognizes TD50 as an international standard for calculating acceptable excess risk. For N-nitroso-dimethylamine, the reported TD50 value for the most sensitive species, the rat, is 0.096 mg/kg/day(Manchuri et al.).

Strategies for mitigating the contamination of n-nitrosamine impurities

Since N-nitrosamine impurities are recognized human carcinogens, strict avoidance of nitrosamine-forming agents such as nitrites, secondary amines, and nitration catalysts during synthesis and manufacturing is essential. This minimizes cancer risk in humans, while regulatory agencies mandate clear guidance to prevent the use of such toxic materials in active pharmaceutical ingredient production (*Hoydonckx,H.E.; VanRhijn,W.M.;VanRhijn,W.; DeVos,D. E.; Jacobs, P. A. Furfural and Derivatives. Ullmann's Encyclopedia of Industrial Chemistry; Wiley, 2007. DOI: 10.1002/ 14356007.A12_119.Pub2.*). Regulatory agencies continuously monitor API synthesis routes and require manufacturers to mitigate risks if N-nitrosamine impurities cannot be fully eliminated. Pharmaceutical companies must implement risk-management plans to safeguard patient safety and ensure impurities remain controlled. Agencies also issue updated guidelines to minimize contamination in both APIs and drug products. These coordinated measures strengthen oversight and protect public health(Manchuri et al.)(*Nasr, N. E. H.; Metwaly, M. G.; Ahmed, E. O.; Fares, A. R.; ElMeshad, A. N. Investigating the Root Cause of N-Nitrosodimethyl Amine Formation in Metformin Pharmaceutical Products. Expert Opinion on Drug Safety; Taylor and Francis Ltd., 2022; Pp 285−287. D*).

Management of Nitrosamine Impurities in Drug Substances

Nitrosamines are recognized as significant impurities that may form in drug substances or pharmaceutical products through the interaction of amines with nitrosating agents. To mitigate the presence of these impurities, the implementation of precautionary measures is essential at various stages of manufacturing(*European Medicines Agency (2019), "EMA Advises Companies on Steps to Take to Avoid Nitrosamines in Human Medicines", Https://Www.Ema.Europa.e u, EMA/511347/2019*).

Nitrosamines can arise from reactions of nitrites with amines during drug manufacturing, making reagent avoidance and restrictions on solvent/catalyst reuse critical. Degradation of raw materials in storage, especially with nitrites, further contributes to impurity formation, necessitating strict storage and testing. Rigorous cleaning and verification of equipment are also essential to prevent cross-contamination(*European Medicines Agency (2019), "Information on Nitrosamines for Marketing Authorization Holders", Https://Www.Ema.Europa.Eu, EMA/189634/2019.*).

Drug manufacturers must adopt robust testing and control strategies to monitor nitrosamine impurities in intermediates and final products. Efficient process optimization to purge amines, nitrites, and nitrosamines is essential to ensure impurities remain within permissible limits.

Effective nitrosamine control requires carefully designed synthesis routes aligned with stringent GMP standards. Proper equipment cleaning and limiting solvent or catalyst reuse are critical to ensure pharmaceutical product safety and quality.

Genotoxicity and Carcinogenicity of Nitrosamines

The majority of nitrosamine contaminants identified in pharmaceuticals thus far are N-nitroso-dialkyl amines. Their genotoxic effects necessitate bioactivation, primarily through hydroxylation mediated by cytochrome P450 enzymes, particularly CYP2E1. An exception is NDEA, which can also undergo bioactivation via CYP2A6(*Yamazaki H, Inui Y, Yun CH, Guengerich FP, Shimada T. Cytochrome P450 2E1 and 2A6 Enzymes as Majorcatalysts for Metabolic Activation of N-Nitrosodialkylamines and Tobacco-Related Nitrosamines in Human Liver Microsomes. Carcinogenesis. 1992;13(10):1789–179*).

The α-hydroxy nitrosamine undergoes spontaneous decomposition, forming an aldehyde and a corresponding alkyl diazohydroxide. This intermediate subsequently generates an alkyl diazonium ion, which then converts into an alkyl carbonium ion. These highly reactive alkylating electrophiles can interact with intracellular nucleophilic macromolecules, such as proteins and DNA, leading to the formation of adducts(*Bellec G, Dreano Y, Lozach P, Menez JF, Berthou F. Cytochrome P450 Metabolic Dealkylation of Nine N-Nitrosodialkylamines by Human Liver Microsomes. Carcino Genesis. 1996;17(9):2029–2034.*)(*Yoo JS, Guengerich FP, Yang CS. Metabolism of N-Nitrosodialkylamines by Human Liver Microsomes. Cancer Res. 1988;48(6):1499–1504*).

In vivo studies have revealed that exposure to NDMA or NDEA results in the formation of methyl and ethyl DNA adducts, predominantly at the N7 position of guanine (N7G), in mouse and rat livers. Alkylation at other sites, including N3A (N3 position of Adenine), O6G (O6 position of Guanine), O2T (O2 position of Thymine), and O4T (O4 position of Thymine), was also observed. Notably, NDEA exhibited a higher ratio of O6G to N7G adducts compared to NDMA, indicating distinct alkylation site distributions for these nitrosamines. These findings underscore the variable genotoxic profiles of NDMA and NDEA.

Due to the severity of carcinogen contamination issues, analysis of N-nitroso-dialkyl amines may eventually need to be integrated into drug specifications for routine quality control(Tuesuwan and Vongsutilers).

Conclusive summary

Nitrosamine impurities represent not only a technical challenge but also a defining test of modern pharmaceutical vigilance. Their detection in widely prescribed medicines has highlighted the fragility of synthetic pathways and the urgent need for proactive safeguards. The convergence of advanced analytical technologies, in-silico predictive tools, and harmonized global regulatory frameworks has created a multidimensional defence against these genotoxic contaminants. Yet, true risk mitigation lies in embedding prevention into the very fabric of drug development through optimized synthesis design, rigorous GMP compliance, and disciplined control of process variables. By integrating scientific innovation with regulatory foresight, the pharmaceutical industry can transform this crisis into a paradigm of resilience, ensuring that patient safety remains uncompromised. Ultimately, the collective response to nitrosamine impurities strengthens not only drug quality but also public trust in medicines as instruments of health and healing.

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