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Review Paper

Nitrosamine Impurities in Pharmaceuticals: Analytical Detection, Risk Assessment, and Quality Control Strategies

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ABSTRACT

Nitrosamine impurities have become one of the most significant pharmaceutical quality and safety concerns since 2018, following widespread detection across multiple therapeutic classes. These genotoxic compounds are potent carcinogens with extremely low acceptable intake limits, generally between 26.6 and 96 nanograms per day, as established under International Council for Harmonization M7 guidelines. Since the discovery of a nitrosamine contaminant in valsartan products manufactured by a Chinese supplier in 2018, regulatory agencies worldwide, including the United States Food and Drug Administration and the European Medicines Agency, have introduced stringent control frameworks and guidance documents. Contamination has since extended beyond angiotensin receptor blockers to metformin, ranitidine, and numerous other drug classes including antimycobacterials, histamine receptor antagonists, statins, ACE inhibitors, anticoagulants, and antidiabetic agents. Modern analytical approaches, particularly liquid chromatography coupled with tandem mass spectrometry, gas chromatography–mass spectrometry, and high-resolution mass spectrometry, now allow detection at sub-parts-per-billion levels with high selectivity. This article reviews nitrosamine chemistry and formation mechanisms, global regulatory frameworks, analytical method development and validation practices, risk assessment methodology, and control strategies applied across the pharmaceutical product lifecycle. The integration of analytical expertise, quality risk management, and regulatory compliance is presented as essential to protecting patient safety while sustaining medicine availability

INTRODUCTION

Nitrosamine impurities are organic compounds bearing the N-nitroso functional group attached to

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two organic substituents. Since 2018 they have drawn unprecedented regulatory and scientific attention because of their potent carcinogenicity and mutagenicity and their potential to contaminate products across many therapeutic classes (1). Their lipophilic character allows cellular membrane penetration, they remain chemically stable under standard storage, and they persist through conventional purification steps, so residual contamination can survive into the finished drug product despite manufacturing controls.

Nitrosamines are classified as Class 1, known genotoxic carcinogens under ICH M7(R1) (1,2,30), and are designated probable human carcinogens (Group 2A) by the International Agency for Research on Cancer (30). Their mechanism of carcinogenicity involves metabolic activation to reactive intermediates that form DNA adducts, producing mutagenic and chromosomal effects. Chronic exposure has been linked to tumors of the liver, lung, nasal cavity, esophagus, pancreas, stomach, bladder, colon, and kidney, and emerging data suggest possible associations with neurodegenerative and metabolic disease.

Although N-nitroso compounds were first described chemically in the 1870s, their toxicological hazard was established by Barnes and Magee in 1956, who demonstrated hepatotoxicity and carcinogenicity in animal models (18). This finding remained largely academic until July 2018, when the FDA recalled valsartan products manufactured by Zhejiang Huahai after detecting unacceptable levels of a nitrosamine contaminant (1,16,18). Recalls quickly extended to losartan and irbesartan in August 2018, affecting roughly sixteen generic manufacturers. Ranitidine was withdrawn globally in September 2019, and metformin recalls followed in December 2019. Contamination has since been identified in rifampicin, varenicline, famotidine, nizatidine, atorvastatin, bumetanide, itraconazole, enalapril, lisinopril, propranolol, duloxetine, rivaroxaban, pioglitazone, gliflozins, cilostazol, and sunitinib, among others.

These incidents exposed vulnerabilities in manufacturing quality systems, raw material sourcing, supplier oversight, and post-approval change control, and revealed that conventional HPLC-UV methods could not detect the trace-level contamination involved (4,21). The low acceptable intake limits, high toxicological potency, and variable formation pathways across manufacturing processes together demand rigorous, lifecycle-wide risk management (25). The aim of this article is to provide holistic review overcurrent nitrosamine chemistry, legislation, analytical methodologies, and risk-based control strategies to aid pharmaceutical quality professionals involved in nitrosamine monitoring and mitigation.

2. CHEMISTRY OF NITROSAMINE IMPURITIES

2.1 Structure and classification

Nitrosamines carry the N-nitroso group attached to two organic moieties, with nitrogen in the +3-oxidation state existing in resonance between nitroxide and diazo tautomers. Secondary amine-derived nitrosamines include N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosomorpholine, N-nitrosopiperidine, and N-nitrosodiisopropylamine. Tertiary amine-derived nitrosamines include N-nitrosoethyl-isopropylamine and the more complex drug substance-related nitrosamines (NDSRIs), which are covalently incorporated into an active pharmaceutical ingredient's molecular scaffold, as seen with nitroso derivatives of valsartan, losartan, telmisartan, and varenicline. Low-molecular-weight volatile nitrosamines are amenable to gas chromatography, while higher-molecular-weight,

non-volatile NDSRIs require liquid chromatography-based approaches.

2.2 Formation mechanism.

Nitrosamine formation requires a nitrosating agent and a secondary or tertiary amine. Nucleophilic attack of the amine's lone pair on an electrophilic nitrosating species, followed by deprotonation, yields the N-nitroso product. Nitrous acid and its anhydride, formed from nitrite under acidic conditions, are the principal nitrosating agents in pharmaceutical settings; nitrogen oxides from combustion or atmospheric sources can also participate. Formation kinetics are markedly enhanced by acidic pH (optimal around pH 1–3), elevated temperature, transition metal catalysis, and high nitrite or amine concentrations.

2.3 Sources of contamination

The predominant source is API synthesis, particularly steps using sodium nitrite for azide displacement in the presence of secondary amine intermediates (1,19). Dimethylamine-containing solvents such as dimethylformamide, dimethylacetamide, and N-methyl pyrrolidone pose risk both through residual traces and through recovered-solvent nitrite carryover. Contaminated raw materials, metal catalysts, and reagents introduce further risk. Excipients, though generally regarded as inert, may carry trace nitrite from their own manufacturing processes, and amino acid-derived excipients introduce additional amine functionality (8,9). Degradation related to storage is well known for ranitidine, where oxidative degradation under heat and humidity leads to the generation of the nitrosamine contaminant during shelf life rather than during manufacture. Packaging materials, including printing inks and elastomeric closures, can also contribute by migration of amine-containing components or photodegradation.

Table 1. Principal nitrosamine formation pathways in pharmaceuticals and associated mitigation strategies

Formation Source	Primary Mechanism	Key Risk Factors	Affected Products	Mitigation Strategy
API synthesis – route design	Nitrite-based reactions (azide displacement)	Acidic pH, heat, metal catalysts, high nitrite	Sartans, metformin, rifampicin	Route redesign; avoid nitrite-based steps
API synthesis – solvent recovery	Recycled amine solvents contaminated with nitrite	Reuse without purification	Multiple amine-based APIs	Nitrite removal; supplier qualification
Raw materials/intermediates	Residual nitrite; amine intermediates	Poor supplier control	Metformin, various excipients	Tight nitrite specifications; supplier audit
Excipients	Nitrite in cellulose derivatives, sugars, amino acids	High nitrite; oxidative stress	Ranitidine, metformin, sartans	Source changes; nitrite specifications
Water and utilities	Atmospheric NOx; municipal residues	Inadequate water system design	Aqueous processing APIs	Water system upgrades; nitrite monitoring

Storage degradation	Oxidative API degradation; nitrite mobilization	Heat, humidity, light	Ranitidine, metformin	Enhanced stability protocols; protective packaging
Packaging materials	Migration of inks/closures; photodegradation	Amine accelerators; light exposure	Light-sensitive formulations	Packaging material changes; light protection

3. TYPES OF NITROSAMINE IMPURITIES

3.1 Volatile nitrosamines

The most frequently detected volatile compounds include N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodiisopropylamine, N-Nitrosodibutylamine, N-nitroso-N-methyl-4-aminobutyric acid, N-nitrosoethyl-isopropylamine, N-nitrosomorpholine, and N-nitrosopiperidine. These are generally well suited to gas chromatography–mass spectrometry, with detection limits in the parts-per-billion to sub-parts-per-billion range.

3.2 API-specific nitrosamines (NDSRIs)

These compounds arise from nitrosation of amine functionality within the API structure itself, requiring dedicated method development because each NDSR is essentially unique to its parent drug. Sartan-derived NDSRIs and nitroso-varenicline are the best-characterized examples; their lower volatility necessitates liquid chromatography–tandem mass spectrometry rather than gas chromatography.

3.3 Comparative potency and acceptable intake

Acceptable intake values are derived from a benchmark dose producing a 10 percent increase in tumor incidence in animal studies, divided by default uncertainty factors, following ICH M7(R1) methodology. Values for commonly detected nitrosamines range from approximately 26.6 nanograms per day for the most potent compounds to 96 nanograms per day for less potent NDSRIs.

4. REGULATORY PERSPECTIVE AND GUIDELINES

4.1 United States Food and Drug Administration

The FDA has implemented a three-step process requiring manufacturers to conduct risk assessments of their products, perform confirmatory testing once risk has been identified, and report findings to the appropriate regulatory agencies (12,16). Its 2019 guidance document on control of nitrosamine impurities in drug products and subsequent guidance on acceptable intake limits of NDSRIs, remain foundational documents and are updated periodically as toxicological knowledge progresses.

4.2 European Medicines Agency

The EMA has a dedicated referral procedure and updated its guidance in July 2023 to include the carcinogenic potency categorisation approach and an enhanced Ames test for determination of acceptable intakes (3,14,15). The European Directorate for the Quality of Medicines and HealthCare has issued parallel scientific categorization frameworks.

4.3 ICH and international harmonization

The ICH M7(R1 guideline classifies nitrosamines as Class 1 impurities, and provides the

internationally accepted methodology for risk assessment and derivation of acceptable intake, with further refinement ongoing through the M7(R2) process (12,13).

4.4 National authorities

Regulatory bodies such as the Therapeutic Goods Administration in Australia, the Medicines and Healthcare Products Regulatory Agency in the United Kingdom, the National Medical Products Administration in China, and ANVISA in Brazil, have issued guidance that is largely consistent with ICH principles, with some jurisdiction-specific requirements (7,8).

4.5 Acceptable intake concept

The acceptable intake is the highest daily exposure that is associated with an acceptable lifetime cancer risk, generally one additional case per 100,000 patients, and is determined by toxicological review, selection of a point of departure, application of uncertainty factors, and consideration of clinical utility (2,12).

Table 2. Acceptable intake limits for selected nitrosamines

Nitrosamine	API Association	FDA AI (ng/day)	EMA AI (ng/day)	ICH M7(R2) Category	Potency
N-Nitrosodimethylamine	Multiple classes	26.5	26.5	Category 1	Very high
N-Nitrosodiethylamine	Multiple classes	26.5	26.5	Category 1	Very high
N-Nitrosodiisopropylamine	Sartans, others	40	40	Category 1	High
N-Nitroso-N-methyl-4-aminobutyric acid	Sartan derivatives	96	96	Category 2	Moderate
N-Nitrosomorpholine	Intermediates	40	40	Category 1	High
N-Nitrosopiperidine	Intermediates	40	40	Category 1	High
N-Nitrosoethyl-isopropylamine	Intermediates	40	40	Category 1	High
N-Nitrosodibutylamine	Intermediates	70	70	Category 1	High
N-Nitroso-valsartan	Valsartan	96	96	Category 2 (NDSRI)	Moderate
N-Nitroso-irbesartan	Irbesartan	96	96	Category 2 (NDSRI)	Moderate
N-Nitroso-losartan	Losartan	96	96	Category 2 (NDSRI)	Moderate
N-Nitroso-varenicline	Varenicline	Interim 60	Interim 60	Category 2 (NDSRI)	Moderate
N-Nitroso-diltiazem	Diltiazem	70	70	Category 1	High
Nitrosamine (degradation)	Ranitidine	26.5	26.5	Category 1	Very high

4.6 Manufacturer obligations

Manufacturers need to carry out risk assessments throughout the product lifecycle, calculate patient exposure, compare exposure to relevant limits, put controls in place, carry out confirmatory testing and communicate findings to regulators (1).

5. ANALYTICAL DETECTION OF NITROSAMINE IMPURITIES

5.1 Analytical challenges

Nitrosamines must be quantified at concentrations several orders of magnitude below conventional impurity specifications, often in the low parts-per-billion range, where instrumental noise and matrix interference become proportionally significant (21,22). Complex pharmaceutical matrices introduce ionization suppression or enhancement in mass spectrometry, particularly from amine-containing APIs and quaternary ammonium excipients (4,22). Nitrosamines are also prone to artefactual formation during sample handling under acidic or oxidizing conditions, and to thermal or photochemical decomposition, requiring careful control of pH, temperature, and light exposure throughout sample preparation (4,20).

5.2 Sample preparation

Solid-phase extraction is the most widely used clean-up method, employing silica-based or polymeric sorbents to trap nitrosamines and eliminate polar excipients and API (21,22). Liquid-liquid extraction is used for aqueous or semi-solid matrices and protein precipitation is used for proteinaceous formulations. Headspace extraction, in which volatile nitrosamines partition into the vapor phase on heating, affords minimal sample handling and largely eliminates matrix effects for small molecule nitrosamines (21). Quality control measures include matrix blanks, solvent blanks, and recovery spiking, usually with a target of 80 to 110 percent recovery.

5.3 Chromatographic techniques.

Reversed-phase HPLC and UPLC using C18 or phenyl columns, with acidic aqueous-organic gradients, form the standard separation approach for non-volatile and polar nitrosamines. UPLC reduces analysis time from twenty to thirty minutes to eight to fifteen minutes but requires more rigorous system suitability protocols.

5.4 Hyphenated mass spectrometry.

LC-MS/MS is the current gold standard, using multiple reaction monitoring to eliminate interference from co-eluting matrix components; typical detection limits fall between 0.01 and 1 part per billion (7,12,27). GC-MS and GC-MS/MS provide orthogonal, volatility-based separation particularly suited to small-molecule nitrosamines (21). Supercritical fluid chromatography-mass spectrometry and capillary electrophoresis-mass spectrometry serve as supplementary techniques for compounds of intermediate polarity or particularly challenging matrices.

5.5 High-resolution mass spectrometry.

Quadrupole time-of-flight and orbital trap instruments provide exact mass measurement and structural elucidation capability, supporting suspect screening and non-targeted discovery of previously uncharacterized NDSRIs (4,5,6).

Table 3. Comparison of analytical techniques for nitrosamine detection

Technique	Analyte Type	LOD/LOQ Range	Sample Prep	Key Advantage	Key Limitation
GC-MS	Volatile nitrosamines	1–50 ppb	Low–moderate	Simple, effective for volatiles	Limited to volatile compounds
HS-GC-MS/MS	Volatile nitrosamines	0.5–10 ppb	Minimal	Matrix elimination	Limited volatile range

LC-MS/MS	All nitrosamines, NDSRIs	0.01–1 ppb	Moderate–high	Gold standard; high selectivity	Matrix effects, ionization suppression
UPLC-MS/MS	All nitrosamines, NDSRIs	0.01–0.5 ppb	Moderate–high	Faster; higher throughput	Higher pressure, solvent use
LC-HRMS	All nitrosamines, unknowns	0.1–5 ppb	Moderate–high	Structural elucidation	Lower sensitivity than MS/MS
GC-MS/MS	Volatile nitrosamines	0.5–5 ppb	Low–moderate	Improved selectivity	Thermal decomposition risk

6. ANALYTICAL METHOD DEVELOPMENT AND VALIDATION

6.1 Method development strategy

Technique selection follows evaluation of volatility, polarity and ionizability, thermal stability, and fragmentation behavior of the target compound. Chromatographic optimization involves stationary phase chemistry, mobile phase pH and composition, and gradient design for LC methods and column phase, oven programming, and injector conditions for GC methods. Mass spectrometric optimization includes ionization source selection, parent and product ion selection, collision energy, and dwell time per transition.

6.2 Validation parameters

Method validation must follow ICH Q2(R2) and USP <1469>, with particular attention to specificity at trace levels, precision near the limit of quantitation, and demonstrated absence of artefactual formation. Internal standards, preferably stable isotope-labelled, are essential to correct for matrix effects and instrument drift.

Table 4. Key validation parameters for nitrosamine analytical methods

Parameter	Typical Acceptance Criteria	Special Consideration
Specificity	No interference at target transition in blank matrix	Matrix-matched blanks; carryover below 20% of LOQ
Linearity	$R^2 \geq 0.99$ across 5–8 points	Range must cover AI-derived specification
Accuracy	80–110% recovery at 50/100/150% levels	Isotope-labelled standards recommended
Precision (repeatability)	RSD ≤15% (≤20% at LOQ)	Critical at trace levels
Precision (intermediate)	RSD ≤15% across days/operators	Environmental variability affects sensitivity
LOD	Signal-to-noise ratio of 3:1	Verified by serial dilution
LOQ	Signal-to-noise ratio of 10:1	Must meet AI-derived specification, typically 0.01–0.1 ppm
Robustness	RSD <15% under parameter variation	Evaluated via fractional factorial design
System suitability	Resolution >1.5; tailing 0.8–1.5	Includes MS tuning verification
Carryover	<20% of LOQ	Assessed after highest standard injection

6.3 Regulatory alignment

Method validation must comply with ICH Q2(R2) and USP <1469> describes four approved methodologies: LC-HRMS, GC-headspace-MS/MS, LC-MS/MS and GC-MS/MS (13,27). The European Pharmacopoeia describes parallel requirements for GC-MS, LC-MS/MS and GC-MS/MS.

7. RISK ASSESSMENT OF NITROSAMINE IMPURITIES

Risk identification starts with a thorough mapping of the process chemistry of each step of the synthesis, focussing on the use of secondary or tertiary amines or nitrite-containing reagents. Tools such as Ishikawa diagrams and failure mode and effects analysis can assist in systematically identifying potential contamination pathways (25). Risk evaluation combines historical batch records, process validation data, and modelling of worst-case scenarios to estimate the likelihood of nitrosamine formation, and exposure assessment combines measured or estimated nitrosamine concentration with daily dose to estimate patient intake. Risk characterization compares estimated exposure to relevant acceptable intake limits, and pathways are classified as high, medium or low risk based on likelihood of occurrence, estimated exposure, and availability of confirmatory analytical methods. Control Strategies are applied in proportion from routine monitoring for low-risk pathways to full process redesign for high-risk pathways.

8. RISK MITIGATION AND CONTROL STRATEGIES

Process chemistry optimization has led several manufacturers to redesign synthesis routes, eliminating bis-amine intermediates and nitrite-dependent transformations in favor of alternative reagents (19). Systematic control of nitrite levels in raw materials, solvents, and process water is fundamental to prevention, supported by supplier qualification and certificate-of-analysis verification (7). Excipient and solvent selection increasingly consider nitrosamine risk alongside functional performance, favoring materials with documented low-nitrite manufacturing histories and avoiding amine-based solvents where alternatives exist (6,9). Packaging materials are evaluated for amine-containing accelerators, inks, and susceptibility to photodegradation, with reformulation or packaging substitution applied where necessary (3). Continuous stability monitoring and routine batch-release testing provide ongoing verification that control strategies remain effective across production batches and suppliers (27).

9. ROLE OF QUALITY ASSURANCE IN NITROSAMINE CONTROL

Quality Assurance functions as the coordinating body translating risk assessment outputs into manufacturing procedures, analytical specifications, and supplier requirements, working across manufacturing, analytical sciences, regulatory affairs, and supply chain management under the ICH Q9 quality risk management framework (25). As a normal part of change control, any changes to the synthesis route, raw material sourcing, process parameters or packaging after approval should have a clear nitrosamine risk assessment (1). Risk assessments, validation data, batch testing results, supplier qualifications and training records should be documented to support regulatory inspection and audit readiness.

10. CASE STUDIES

The sartan contamination crisis, which started in 2018, was triggered by a change in the synthesis route that introduced an azide-elimination step

with sodium nitrite under acidic conditions, leading to nitrosamine contamination that was not detected in several batches due to insufficient analytical sensitivity (18). The event exposed systemic failures in process understanding, change control, analytical capability and supplier oversight and led to recalls across some sixteen manufacturers.

Ranitidine had a different mechanism, with nitrosamine formation being caused by oxidative degradation of the secondary amine functionality of the API during storage at elevated temperature and humidity, not during manufacture (18). This finding proved that even well-controlled manufacturing did not guarantee long-term product safety without corresponding attention to storage conditions and shelf-life limitations.

Metformin contamination affected multiple manufacturers globally and was traced to nitrite contamination in raw materials or synthesis intermediates, again detected only once sensitive LC-MS/MS methods were developed in response to regulatory mandates (18). Continued vigilance has since identified contamination across an expanding range of therapeutic classes, each requiring individualized regulatory and manufacturing response (5,16).

FUTURE PERSPECTIVES

Continued identification of structurally novel NDSRIs will require dedicated toxicological characterization and analytical method development for each new compound (4,5). Analytical advances are expected to focus on ultra-high-sensitivity methods approaching the parts-per-trillion range, non-targeted screening using high-resolution mass spectrometry, and high-throughput methodologies suited to large-scale surveillance (21,27). Regulatory structures will keep evolving as toxicological data accumulate and international harmonization efforts progress (2,14). The broader shift toward lifecycle risk management, integrating development-stage process understanding with post-approval monitoring, represents a lasting change in pharmaceutical quality practice (25).

CONCLUSION

Nitrosamine impurities remain among the most consequential pharmaceutical quality challenges of the present era, with contamination documented across numerous therapeutic classes and affecting patients worldwide. Effective control requires integration of advanced analytical chemistry, mechanistic understanding of formation pathways, rigorous process control, and proactive regulatory engagement. LC-MS/MS, GC-MS, and HRMS technologies now enable detection at the sub-parts-per-billion levels demanded by current regulatory standards, provided that method development and validation strictly follow ICH Q2(R2) and USP <1469>. The continuing shift toward risk-based, lifecycle-wide quality management offers the most durable path toward sustained nitrosamine control and patient safety.

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