Asian Journal of Pharmaceutical and Health Sciences
http://www.ajphs.com
ISSN: 2231- 2331(Print) | ISSN: 2231–234X(Online)

Mini Review

Emerging Concerns of Nitrosamine Impurities in Drug Perspectives

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Article History
Received :01.08.2025
Revised :11.09.2025
Accepted :20.09.2025

DOI

10.5530/ajphs.2025.15.85

Keywords
Nitrosamine
N-nitrosodimethylamine
carcinogens
FDA

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ABSTRACT

Nitrosamine impurities have emerged as a global pharmaceutical concern since the detection of N-nitrosodimethylamine (NDMA) in valsartan in 2018. Recognised as probable human carcinogens, nitrosamines have since been identified in several essential drugs, including ranitidine, metformin, and ARBs (Angiotensin II Receptor Blockers), prompting large-scale recalls, regulatory investigations, and significant industry impact. Their presence is primarily linked to synthesis pathways, contaminated raw materials, degradation processes, and interactions with packaging. This review discusses the chemical nature of nitrosamines, their formation mechanisms, case studies, analytical methods for detection, and current regulatory frameworks from the FDA, EMA, and ICH. Risk assessment strategies, industry responses, and future perspectives for robust impurity management are also explored.

1. INTRODUCTION

Nitrosamine impurities have emerged as one of the most critical quality and safety concerns in the global pharmaceutical industry over the past decade (Dakhole et al., 2023). Historically, nitrosamines were first identified as potent carcinogens in food and tobacco products during the 1950s, formed by reactions between amines and nitrites under acidic or thermal conditions (Lijinsky, 1999). Yet their sudden appearance in pharmaceuticals, first in 2018 when N-nitrosodimethylamine (NDMA) was found in the antihypertensive drug valsartan, was a watershed moment in drug safety regulation (European Medicines Agency, 2025). It led to mass recalls across several nations, affecting millions of patients and prompting unprecedented regulatory investigations (Hao et al., 2024).

Nitrosamines are likely human carcinogens (IARC Group 2A) that can cause DNA alkylation and oxidative stress, leading to gene mutation and tumour growth (Manchuri & Shaik, 2024). Their chronic exposure at trace levels poses significant health hazards, warranting rigorous control and testing during the production of pharmaceuticals (Vikram et al., 2024). Later findings of nitrosamines in ranitidine,

metformin, losartan, and other medicines brought into focus the multifactorial causes of these impurities, which ranged from synthetic routes and carryover solvents to impurities arising from excipients and degradation processes during storage (Ranganathan et al., 2024; Sedlo et al., 2021).

In response, international regulatory bodies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) have released broad guidance to set acceptable intake levels, require root-cause analyses, and standardise analytical techniques for detecting nitrosamines (U.S. Food and Drug Administration, 2024 World Health Organization, 2019). Short of these measures, predicting and preventing nitrosamine formation across a wide range of formulations and manufacturing processes remains problematic (BioPharmaSpec, 2023).

This review will discuss peripheral nitrosamine contaminants in pharmaceuticals. The article also highlights recent advances in risk assessment, predictive modelling, and control measures that contribute to safer, more environmentally friendly drug development processes (Vikram et al., 2024; Zheng et al., 2024).

2. CHEMICAL BACKGROUND OF NITROSAMINES

Nitrosamines are a group of chemicals whose general structure is $R_2N–N=O$, in which two alkyl or aryl groups are attached to a nitroso functional group (Dakhole et al., 2023; BioPharmaSpec, 2023). Their generation usually results from nitrosation reactions involving the interaction of secondary or tertiary amines with nitrosating agents such as nitrite ions in acidic or oxidative media (Manchuri & Shaik, 2024). Environmental conditions strongly control their formation; mainly pH, temperature, and residual solvents such as dimethylformamide or dimethylamine, which may act as precursors or catalysts (Ranganathan et al., 2024).

In drug manufacturing, nitrosation may happen by accident during synthesis, purification, or storage processes (Sedlo et al., 2021). Trace amounts of nitrite impurities in excipients, raw material, or even process water could trigger these reactions, especially when amine-containing intermediates are present (Hao et al., 2024). Also, certain formulation conditions, such as higher temperatures or light exposure, can favour the formation of nitrosamines, especially in tertiary amines or amide-containing products (PerkinElmer, 2023).

Metabolic activation of nitrosamines, from a mechanistic perspective, is mainly mediated by cytochrome P450 enzymes, resulting in electrophilic alkyl diazonium intermediates that bind to DNA and trigger mutagenic processes (Lijinsky, 1999). To forecast such hazards in drug design, current computational techniques, such as quantitative structure–activity relationship (QSAR) models, machine learning models, and ICH M7 (R2)-compliant predictive models, are being used more and more to scan prospective nitrosamine precursors and inform safer synthetic route designs (Vikram et al., 2024).

3. SOURCES OF NITROSAMINE CONTAMINATION IN PHARMACEUTICALS

Nitrosamine contamination of drug products can arise from a variety of interrelated pathways during the manufacturing and storage procedures (Ranganathan et al., 2024). The most direct source exists in active pharmaceutical ingredient (API) synthesis, in which secondary or tertiary amines, amide solvents, or nitrite reagents are used to unintentionally initiate nitrosation reactions (Dakhole et al., 2023). An example is where sodium nitrite is applied in the presence of acidic media during API synthesis, or where solvents like dimethylformamide (DMF) or dimethylacetamide (DMA) are utilised, trace amines could be activated with nitrosating agents to produce nitrosamines like NDMA or NDEA (BioPharmaSpec, 2023; Hao et al., 2024). Inadequate purification or inaccurate control of process intermediates further exacerbates this risk (Manchuri & Shaik, 2024).

Cross-contamination is also a significant issue, especially in facilities where various products are manufactured using common reactors or equipment (Sedlo et al., 2021). Without proper cleaning, trace amounts of amine-based compounds or nitrites can carry over and react in subsequent production cycles, leading to unintended nitrosamine formation (Ranganathan et al., 2024). Regulatory guidelines now require strict equipment segregation and cleaning procedures to prevent such cross-contamination (U.S. Food and Drug Administration, 2024).

Product degradation is another significant contributor, particularly in amine-containing pharmaceuticals (Hao et al., 2024). For instance, ranitidine and metformin are recognised to form NDMA during prolonged storage or upon heat treatment due to internal rearrangements and functional group decomposition (Health.com, 2022). This degradation mechanism underscores the importance of conducting stability tests over extended periods under controlled conditions (PerkinElmer, 2023). Packaging materials may also contribute.

Nitrocellulose-containing blister packs and some rubber stoppers have been found to release nitrosating species that react with drug molecules or excipients, especially at humid or elevated temperatures Such as Raw materials and excipients such as talc, magnesium stearate, and contaminated process water may contain trace amounts of nitrites, which can induce unwanted nitrosation reactions (Ranganathan et al., 2024).

Thus, detection and management of these disparate sources through raw material qualification, stringent analytical screening, and compliance with Good Manufacturing Practices (GMP) are critical to reducing nitrosamine risk throughout the pharmaceutical drug production process (Dakhole et al., 2023; BioPharmaSpec, 2023).

4. CASE STUDIES OF NITROSAMINE CONTAMINATION

Several high-profile incidents over the last decade have documented the pervasive, multicausal nature of nitrosamine contamination in pharmaceuticals (Dakhole et al., 2023; Manchuri & Shaik, 2024). The initial serious incident was in 2018, when N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) impurities were found in valsartan, an angiotensin II receptor blocker (ARB) (Hao et al., 2024; U.S. Food and Drug Administration, 2024). Investigations concluded that the impurities were due to the use of sodium nitrite and dimethylformamide (DMF) in the route of API synthesis (BioPharmaSpec, 2023; PerkinElmer, 2023). The finding led to worldwide recalls, underscoring the vulnerability of intricate supply chains and the importance of improved impurity profiling (Ranganathan et al., 2024).

It was followed in 2019 by the discovery of NDMA contamination in ranitidine, a popular histamine-2 receptor antagonist (Health.com, 2022). In contrast to valsartan, where contamination resulted from the synthesis process itself, ranitidine's problem was due to intrinsic degradation: the drug's chemical structure allowed NDMA formation during storage, particularly under heat and moisture (Sedlo et al., 2021). it led to worldwide regulatory withdrawals by bodies such as the U.S. FDA and the EMA (U.S. Food and Drug Administration, 2024).

In 2020, metformin, a first-line antidiabetic drug, was another subject of criticism when extended-release products tested positive for NDMA levels higher than the daily intake limit allowed (World Health Organization, 2019). Investigations indicated several sources, ranging from contaminated excipients to breakdown under certain manufacturing conditions (Ranganathan et al., 2024; Hao et al., 2024).

Additional instances involving losartan, irbesartan, and rifampicin established that the nitrosamine contamination was not limited to a single drug class or manufacturer (Vikram et al., 2024). Sitagliptin tablets in Japan contained a new nitrosamine impurity, N-nitroso-STG-19, highlighting the changing sophistication of the problem (Hao et al., 2024; Loganathan et al., 2025).

These case histories, when considered together, highlight the need for proactive risk evaluation, predictive modelling, and regular monitoring of nitrosamines throughout the drug lifecycle from raw material sourcing to final product stability (PerkinElmer, 2023; Vikram et al., 2024). Each event has added valuable lessons that have since shaped more stringent regulatory principles and enhanced quality control systems worldwide (U.S. Food and Drug Administration, 2024; European Medicines Agency, 2025).

5. ANALYTICAL METHODS FOR DETECTION OF NITROSAMINES

Nitrosamine impurities in drugs pose serious analytical challenges for detection, as they are typically present at low concentrations (in the parts-per-billion range) and exist in a chemically labile form (BioPharmaSpec, 2023; Manchuri & Shaik, 2024). Precise and sensitive assays are thus indispensable in their identification and quantification in both finished drug products and active pharmaceutical ingredients (APIs) (Hao et al., 2024) (Table 1).

Among available techniques, Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) is the most widely adopted method, combining efficient chromatographic separation with high detection sensitivity (BioPharmaSpec, 2023; PerkinElmer, 2023). This technique allows for simultaneous quantification of multiple nitrosamines, including NDMA, NDEA, NMBA, and NEIPA, across diverse matrices (Hao et al., 2024). LC-MS/MS methods are often preferred for their robustness, low detection limits, and compliance with global regulatory requirements (U.S. Food and Drug Administration, 2024).

Gas Chromatography–Mass Spectrometry (GC-MS) remains highly effective for analysing volatile nitrosamines such as NDMA and NDEA (Sedlo et al., 2021). Derivatisation steps may be required for non-volatile compounds, though this approach offers exceptional specificity and reproducibility. Meanwhile, High-Resolution Mass Spectrometry (HRMS) provides structural elucidation and accurate mass determination,

Table 1: Analytical methods for the detection of nitrosamines

Method	Principle	Advantages	Limitations / Example Use
LC-MS/MS	Liquid separation + MS/MS	High sensitivity, simultaneous detection	Requires specialised equipment; NDMA in valsartan, metformin (PerkinElmer, 2023)
GC-MS	Gas separation + MS	Excellent for volatile nitrosamines	Non-volatile compounds need derivatisation NDMA in ranitidine (Sedlo et al., 2021)
HRMS	Accurate mass measurement	Confirms unknown structures	Expensive; Identification of new nitrosamines (Zheng et al., 2024)
NMR	Nuclear resonance spectroscopy	Structural information, non-destructive	Low sensitivity for trace levels; Supports structural confirmation (Manchuri & Shaik, 2024)

making it valuable for identifying previously unknown nitrosamines (Zheng et al., 2024). Nuclear Magnetic Resonance (NMR) spectroscopy, though less sensitive, plays an important confirmatory role in verifying molecular structures of detected impurities (Manchuri & Shaik, 2024).

Sample preparation techniques such as solid-phase extraction (SPE) and liquid–liquid extraction (LLE) are commonly used to concentrate analytes and minimise matrix interferences (Hao et al., 2024). These methods, when coupled with mass spectrometry, achieve detection limits of 0.3–1 ppb (PerkinElmer, 2023). Analytical method validation, following ICH and FDA guidelines, ensures precision, accuracy, linearity, and reproducibility (U.S. Food and Drug Administration, 2024).

Recent advancements include the use of two-dimensional LC systems and headspace GC-MS to improve selectivity and throughput (BioPharmaSpec, 2023). The integration of computational modelling and artificial intelligence (AI) has also enhanced analytical workflows by predicting likely nitrosamine structures, streamlining the identification of potential contaminants (Vikram et al., 2024). Together, these developments enable a more proactive and sensitive approach to impurity surveillance in pharmaceutical quality control (Loganathan et al., 2025; Hao et al., 2024).

6. REGULATORY GUIDELINES AND LIMITS

The global discovery of nitrosamine impurities has triggered a series of comprehensive regulatory interventions aimed at safeguarding patient health and maintaining pharmaceutical quality (U.S. Food and Drug Administration, 2024; European Medicines Agency, 2025; World Health Organization Prequalification Team, 2019). Major authorities, including the FDA, EMA, and International Council for Harmonisation (ICH), have established harmonised frameworks for identifying, assessing, and mitigating nitrosamine contamination throughout the drug lifecycle (ICH M7(R2), 2022; PerkinElmer, 2023).

The FDA's 2021 guidance defines acceptable daily intake (ADI) limits for key nitrosamines, details methodologies for risk assessment, and emphasises root-cause evaluation to eliminate contamination pathways (U.S. Food and Drug Administration, 2024; Food and Drug Administration, 2025). Similarly, the EMA's 2020 directive requires confirmatory testing for all chemically synthesised and biological products that may contain secondary or tertiary amines, ensuring that nitrosamine levels remain within defined safety thresholds (European Medicines Agency, 2025; European Medicines Agency, n.d) (Table 6).

The ICH M7 (R2) guideline integrates nitrosamines into the broader category of mutagenic impurities, promoting structure–activity relationship (SAR)-based assessments and predictive computational modelling (ICH M7(R2), 2022; Loganathan et al., 2025). These principles have been globally adopted by the WHO and national agencies such as Japan's PMDA and Singapore's HSA, ensuring international alignment in safety standards (World Health Organization Prequalification Team, 2019).

Manufacturers are now required to perform confirmatory testing within specified timelines and take corrective actions if nitrosamine levels exceed permissible ADIs (e.g., 96 ng/day for NDMA, 26.5 ng/day for NDEA/NEIPA, and 37 ng/day for NTTP) (U.S. Food and Drug Administration, 2024; European Medicines Agency, 2025). Collectively, these coordinated measures have strengthened global surveillance systems and underscored the industry's shared responsibility to safeguard patient safety against genotoxic impurities (Vikram et al., 2024).

Table 1: Nitrosamine impurities, acceptable intake limits, and examples of affected drugs

Nitrosamine	ADI (ng/day)	Example Affected Drugs
NDMA	96	Valsartan, Metformin, Ranitidine
NDEA	26.5	Valsartan, ARBs
NMBA	96	Losartan, sartan-family APIs
NDIPA	26.5	Sartan APIs

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7. INDUSTRY IMPACT

The nitrosamine crisis has deeply influenced the pharmaceutical industry, affecting economics, operations, and public confidence (Vikram et al., 2024; Ranganathan et al., 2024). Large-scale recalls, analytical retesting, and process redesigns have collectively cost manufacturers billions of dollars and disrupted supply chains (Hao et al., 2024; Dakhole et al., 2023). The need for alternative synthesis pathways and revalidation of existing processes has delayed drug availability and regulatory approvals (PerkinElmer, 2023).

In response, companies have strengthened Quality-by-Design (QbD) frameworks, established dedicated facilities for high-risk compounds, and enhanced supplier oversight (Vikram et al., 2024). The crisis also emphasised the importance of global data sharing between regulators and manufacturers to accelerate remediation efforts (European Medicines Agency, 2025). Public perception, particularly of generic drugs, was initially damaged; however, the event catalysed innovation, driving the adoption of AI-based risk assessment models and predictive impurity profiling tools (Loganathan et al., 2025; Hao et al., 2024). Ultimately, while disruptive, the crisis advanced the industry toward more preventive, science-driven quality management systems (Vikram et al., 2024).

8. RISK ASSESSMENT AND CONTROL STRATEGIES

Comprehensive control of nitrosamine impurities begins with identifying potential formation pathways during synthesis or degradation (Ranganathan et al., 2024; Manchuri & Shaik, 2024). Structural alerts—such as secondary and tertiary amines—must be evaluated in combination with nitrite sources, solvents, and process conditions (BioPharmaSpec, 2023; Sedlo et al., 2021).

Synthetic redesign remains one of the most effective mitigation strategies. Adjusting reaction conditions, replacing nitrite reagents, or using alternative solvents can significantly reduce nitrosation potential (PerkinElmer, 2023). Ensuring high-purity raw materials and reliable suppliers further minimises external contamination risks (Hao et al., 2024).

At the facility level, dedicated equipment, validated cleaning procedures, and waste segregation help prevent cross-contamination (Vikram et al., 2024). Packaging innovations, including the avoidance of nitrocellulose-based materials, provide an additional layer of protection (Sedlo et al., 2021). Emerging AI and computational models now allow early prediction of nitrosamine risk based on molecular structure and process parameters (Loganathan et al., 2025; Hao et al., 2024). Continuous monitoring through LC-MS/MS or GC-MS ensures ongoing compliance (BioPharmaSpec, 2023; PerkinElmer, 2023). Collaborative regulatory reporting and harmonised standards remain critical for maintaining transparency and preventing future incidents (U.S. Food and Drug Administration, 2024; European Medicines Agency, 2025).

9. FUTURE PERSPECTIVES

Future strategies for nitrosamine control will rely heavily on innovation in both analytics and manufacturing science (Hao et al., 2024; Loganathan et al., 2025). Ultra-sensitive analytical platforms capable of sub-ppb detection will enhance precision and throughput (BioPharmaSpec, 2023). Artificial intelligence and machine learning will play central roles

in predicting nitrosamine formation, evaluating process vulnerabilities, and optimising synthesis design (Vikram et al., 2024).

The adoption of green chemistry principles, including solvent-free synthesis and biocatalytic transformations, will further reduce nitrosation risks while promoting sustainability (Ranganathan et al., 2024). Globally, joint regulatory inspections, data-sharing frameworks, and harmonised impurity databases are expected to strengthen cooperation (European Medicines Agency, 2025; World Health Organization Prequalification Team, 2019).

Ultimately, lessons from recent contamination events will guide the creation of a more resilient pharmaceutical ecosystem in which nitrosamine formation becomes scientifically predictable and technologically preventable (Vikram et al., 2024; Hao et al., 2024).

10. CONCLUSION

Nitrosamine impurities have redefined pharmaceutical quality management, emphasising the need for robust impurity profiling, proactive risk assessment, and transparent regulatory collaboration (U.S. Food and Drug Administration, 2024; European Medicines Agency, 2025). The sequence of contamination events involving valsartan, ranitidine, and metformin exposed critical weaknesses in manufacturing oversight (Hao et al., 2024; Dakhole et al., 2023).

Ongoing advancements in analytical science, regulatory harmonisation, and predictive AI modelling have enhanced industry readiness, yet total prevention remains a continuing challenge (Loganathan et al., 2025; Vikram et al., 2024). Sustained cooperation among regulators, manufacturers, and researchers is vital to uphold patient safety (World Health Organization, 2019).

In essence, the nitrosamine episode represents a pivotal turning point—transforming impurity control from a reactive process into a proactive, science-based discipline that safeguards global drug integrity (Ranganathan et al., 2024; PerkinElmer, 2023).

List of Abbreviations

ADI	Acceptable Daily Intake
API	Active Pharmaceutical Ingredient
ARB	Angiotensin II Receptor Blocker
GC-MS	Gas Chromatography–Mass Spectrometry
HRMS	High-Resolution Mass Spectrometry
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
NDEA	N-Nitrosodiethylamine
NDMA	N-Nitrosodimethylamine
NMBA	N-Nitroso-N-methyl-4-aminobutyric acid
NDIPA	N-Nitroso-diisopropylamine
NEIPA	N-Nitroso-ethylisopropylamine
NTTP	N-Nitroso-tri-tert-butylamine
NDSRI	Nitrosamine Drug Substance Related Impurities

Acknowledgements

The authors would like to thank the institution for its support for this study.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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Cite this article: Amritesh Kumar, Aryan Garaye, Satyam, Anurag Vikram, Uddhav Bhambure, Mueed Dar, Rajesh Rane. Emerging Concerns of Nitrosamine Impurities in Drug Perspectives. Asian J. Pharm. Health. Sci.. 2025;15(3):3133-3139. DOI:10.5530/ajphs.2025.15.85