NITROGENOUS COMPOUNDS AS CONTAMINANTS OF HEALTH CONCERN

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Discussion

Nitrogenous compounds are chemical substances to which humans have been constantly exposed. In many cases, they go unnoticed by the general population until high-magnitude events occur, such as massive product recalls from the market. Although pharmaceutical and food technology has evolved significantly, these compounds continue to represent a challenge regarding their detection, identification, and quantification.

Factors such as the limited availability of analytical methods with the necessary specificity to guarantee their determination, as well as the need for high-sensitivity equipment for their separation and detection—which also require considerable investment—are part of the challenges that regulatory agencies must overcome to achieve adequate control of these types of impurities.

Nitrogenous compounds, particularly nitrosamines, have been linked to the development of oncological diseases, which represent one of the primary public health challenges globally. Currently, robust scientific evidence demonstrates a clear association between various types of tumors and multiple risk factors—including tobacco use, dietary habits, alcohol consumption, and exposure to carcinogenic chemical agents, among which nitrogenous compounds are categorized.

Keywords: nitrogenous compounds, N-nitrosamines, nitrogenous impurities, carcinogens, mutagens

In El Salvador, while nitrogenous compounds and nitrosamines are recognized within scientific, pharmaceutical, and regulatory circles, it is essential that foundational information regarding these substances and their primary routes of exposure be disseminated to the general population.

To address this, a documentary investigation was conducted through a systematic review of official sources, including the United States Pharmacopeia (USP), as well as data published by international organizations such as the World Health Organization (WHO).

Risk assessments issued by food safety authorities, such as the European Food Safety Authority (EFSA), were also analyzed. Furthermore, scientific articles from reputable publishers, including Elsevier, were consulted.

These sources provided comprehensive data on nitrogenous compounds—specifically nitrosamines—encompassing their definitions, formation mechanisms, prevalence across various matrices, the clinical significance of their detection, and the specialized methodologies and analytical instrumentation required for their determination.

The literature search period spanned from February 20, 2025, to January 30, 2026. Inclusion criteria for scientific articles required publication between 2015 and 2025, with no restrictions on study design (e.g., reviews, observational, or experimental studies).

Search keywords, which also served as the study variables, included: nitrosamines, nitrosamines in pharmaceuticals, nitrosamines in food and beverages, nitrosamines in tobacco, nitrosamines and alcoholism, and the formation of nitrogenous compounds in food. As exclusion criterion,

entific articles focusing on matrices outside the established scope were discarded. Ultimately, studies deemed aligned with the objective of this review were selected for analysis.

Nitrosamines (N-nitrosamines)
According to WHO, N-nitrosamines are molecules containing a nitroso functional group that provoke significant concern because their impurities may be carcinogenic to humans. While they can be found in certain foods and drinking water supplies, their presence in pharmaceutical products is considered unacceptable from a regulatory standpoint. Generally, within the pharmaceutical context, they are formed when a secondary or tertiary amine reacts with nitrous acid—an unstable acid that can be generated from nitrites (NO_2^-) in acidic media.

Official compendia explicitly define the risks associated with these contaminants. For instance, USP states that "N-nitroso compounds are among the structural groups of high-potency mutagenic carcinogens for various animal species," and ICH M7 guideline classifies specific analogues as probable or possible human carcinogens, labeling them as a "cohort of concern" (United States Pharmacopeia, 2025).

In the food and beverage sector, nitrosamines present a unique complexity. The most recognized related substances are nitrates and nitrites—inorganic nitrogen-derived compounds found naturally in vegetables and utilized as additives in processed meats. Their presence in the human diet has been linked to oncogenesis due to their capacity to undergo endogenous transformation into N-nitrosamines (Pereira & Davahiva Gómez Ramírez, 2011). Furthermore, International Agency for Research on Cancer (IARC) classifications describe the strength of scientific evidence regarding whether an agent causes cancer, rather than assessing the specific level of risk for an individual (WHO, 2015).

Nitrosamines in Pharmaceuticals
The presence of nitrosamine impurities in medicinal products triggered a global alert following their detection in 2018 in drugs such as valsartan. This crisis compelled manufacturers to reassess synthetic pathways and develop rigorous analytical methodologies for their detection. Among the medications implicated in the 2018 alert were valsartan, pioglitazone, and ranitidine, as well as nizatidine and metformin (Zayra Flores García, 2024).

As investigations progressed, additional impurities with potential carcinogenic risk were identified (USP, 2025). Emerging impurities included N-nitrosoethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA), and N-nitroso-N-methyl-4-aminobutyric acid (NMBA). Consequently, the FDA established a consumption parameter known as the Acceptable Intake (AI) for nitrosamines in pharmaceuticals. These regulatory thresholds led to the withdrawal of several products from the market, most notably ranitidine (Zayra Flores García, 2024).

Sources of Nitrosamines in Medicinal Products
The formation of nitrosamines in pharmaceuticals can arise from diverse sources throughout the manufacturing process or the product's life cycle. A primary cause is the chemical reaction of secondary or tertiary amines with nitrites under acidic conditions. Furthermore, nitrosamines may form as a result of the degradation of the active pharmaceutical ingredient (API)—such as ranitidine—or within the finished dosage form due to reactions within the formulated matrix.

The degradation of solvents like dimethyl formamide (DMF), inadequate recycling processes, cross-contamination, or poor solvent quality can also contribute to nitrosamine generation. Other significant sources include impurities present in raw materials, solvents, reagents, or catalysts, as well as contaminants in the water utilized during manufacturing. Excipients represent an additional potential source, either through the direct presence of nitrosamines or the introduction of nitrosating agents.

Specific reaction conditions during the manufacturing process may further favor their formation. Finally, the container closure system and primary packaging materials of the finished product can serve as a source, particularly when they contain amines or materials associated with nitrosating agents, such as nitrites or nitrocellulose.

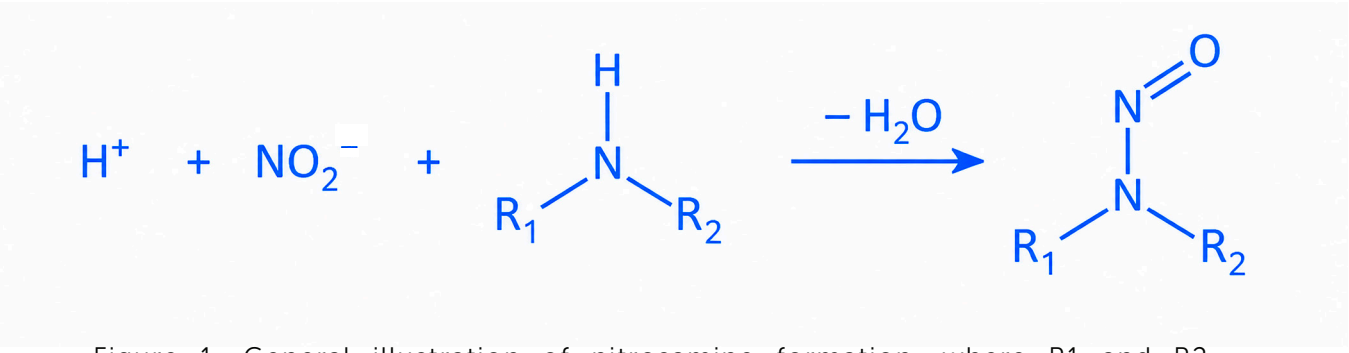

Figure 1. General illustration of nitrosamine formation, where R1 and R2 represent alkyl or functionalized alkyl groups (only one of which may be an aryl or functionalized aryl group). (United States Pharmacopeia, 2025)

Nitrosamines in Food and Beverages

Natural or synthetic preservatives are added to food products to extend shelf life, maintain quality, and ensure safety by inhibiting processes such as fermentation, acidification, decomposition, and microbial contamination. However, the addition of synthetic chemical preservatives can increase the risk of nitrosamine exposure, as nitrites and nitrates are integral components of this group.

Nitrogenous compounds, specifically nitrates and nitrites, are found in vegetables, fruits, and legumes. These originate from agricultural production via ammonium fertilizers, animal manure, leguminous residues, pest control chemicals, and irrigation water absorbed by plants.

The concentration of these compounds depends on factors such as soil composition, fertilization practices, temperature, sunlight, water availability, and storage or processing conditions. It is estimated that 85% of daily nitrate intake comes from vegetables, with radishes, lettuce, beets, and spinach exhibiting the highest concentrations.

Nitrosamines and their precursors are prevalent in processed meats and fish, as well as in beer and tobacco. Nitrates and nitrites in food act as precursors that can metabolically combine with amines to form nitrosamines.

The N-nitroso compounds most frequently identified in food matrices include N-nitrosodimethylamine (NDMA), N-nitrosopyrrolidine (NPYR), N-nitrosopiperidine (NPIP), and N-nitrosothiazolidine (NTHZ). These are primarily formed during the production of processed meats as a direct consequence of adding nitrate/nitrite salts (Pereira & Davahiva Gómez Ramírez, 2021).

Foods that increase cancer risk

Red and processed meats

Red meat refers to all mammalian muscle meat, including beef, veal, pork, lamb, mutton, horse, and goat. Processed meat is defined as meat transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation. Both red meat (Group 2A) and processed meat (Group 1) are primarily linked to colorectal cancer, with potential associations to pancreatic and prostate cancers (WHO, 2015). Processed products such as ham, bacon, salami, sausages, and industrial burgers contain precursors that facilitate the formation of potentially carcinogenic nitrosamines (Svatetz, 2024).

Alcoholic beverages

The association with carcinogenic tumors depends on the volume and frequency of consumption. Across all tumor types, an association exists with all categories of alcoholic beverages, as they all contain ethanol, the primary causative agent of cancer. It is critical to emphasize that regarding oncogenic effects, there is no level of alcohol consumption that can be considered safe or harmless. This is due to an established dose-response relationship; while a lower dose may result in a lower risk, an effect is always present.

Tobacco and Nicotine-Related Products

Tobacco use is extensively linked to oncogenesis. Emerging consumption formats, such as nicotine pouches, also present significant public health risks due to the presence of potentially deleterious nitrogenous compounds.

Ultra-Performance Liquid Chromatography coupled with Triple Quadrupole Mass Spectrometry (UPLC-MS/MS) constitutes a viable analytical strategy to achieve the necessary sensitivity for these analytes. However, this approach needs the rigorous development

and validation of methods tailored to the specific impurities and the selected matrix. Furthermore, it is essential to establish precise detection parameters and sample preparation protocols to mitigate the risk of cross-contamination (Zayra Flores García, 2024; Romero et al., 2024).

Since no official monographs currently exist for the determination of nitrosamines as impurities within specific finished pharmaceutical forms—relying instead on general chapters that provide high-level recommendations and considerations—method validation must be comprehensive. It must incorporate system suitability parameters such as precision, linear range, and working range, alongside method-specific parameters including specificity, accuracy, linearity, limits of detection (LOD) and quantification (LOQ), and repeatability. These procedures must strictly align with official compendial standards, such as USP General Chapter <1225>, Validation of Compendial Procedures (Ayala Lara, 2024; USP, 2025).

The current trend in quality assurance laboratories regarding analytical methodologies is Analytical Quality by Design (AQbD). The primary objective of this framework is to build quality into the results starting from the initial design of the method, grounded in scientific principles and risk management.

In the specific case of nitrosamines, while compendial methods exist for determination in raw materials, their application to finished products remains limited. To address these gaps, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) adopted the Q14 Guideline in 2023, titled "Guideline on Analytical Procedure Development," which facilitates the implementation of AQbD.

Among the prominent methodologies for nitrosamine determination, Liquid Chromatography coupled with Mass Spectrometry (LC-MS) stands out due to its high accuracy, precision, robustness, and extreme sensitivity—capable of reaching levels in the parts per billion (ppb) range. This technology has been successfully validated for the determination of at least five nitrosamines identified by the FDA as potential contaminants in medicinal products (NDMA, NMBA, NDEA, NEIPA, and NDIPA), with specific efficacy demonstrated in complex matrices such as losartan tablets (Lutton, M., 2025).

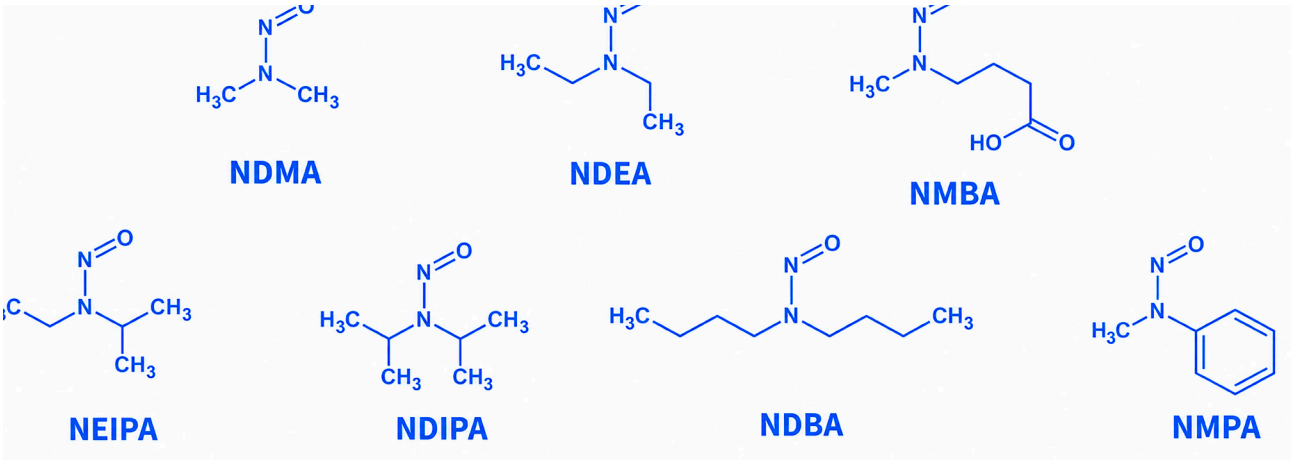

Figure 2. Chemical structures of the seven small-molecule nitrosamine impurities identified by the FDA that could theoretically be present in pharmaceutical products (Lutton, M., 2025)

Furthermore, there is empirical evidence regarding the development and validation of LC-HESI-MS/MS (Liquid Chromatography with Heated Electrospray Ionization and Tandem Mass Spectrometry) methods that are robust, efficient, and sensitive. These methods allow for the simultaneous detection and quantification of five N-nitrosamines: N-nitrosodimethylamine, N-nitrosodiisopropylamine, N-nitrosodibutylamine, N-nitrosopyrrolidine, and N-nitroso-methyl-4-aminobutyric acid. In evaluations of N-nitrosamine recovery in valsartan, recovery values ranged between 70% and 130%, while repeatability and intermediate precision demonstrated coefficients of variation below 10%, even when assessed in a complex drug product containing three active pharmaceutical ingredients: Amlodipine, Hydrochlorothiazide, and Valsartan (Reina-Velasco, C., 2024).

The presented results demonstrate that the presence of nitrosamines is intrinsically linked to chemical synthesis processes, degradation of active ingredients, storage conditions, and the composition of food and pharmaceutical matrices. The 2018 valsartan incident marked a critical turning point in international regulation, proving that even minor variations in manufacturing routes can generate impurities with significant toxicological impact.

Similarly, the degradation observed in drugs such as ranitidine highlighted the necessity of considering not only the initial synthesis phase but also the stability of the product during storage and throughout its shelf life. This underscores the need for comprehensive risk assessments that encompass raw materials, excipients, environmental conditions, and potential chemical interactions within the finished formulation.

In the food sector, the findings suggest that nitrosamine exposure may be cumulative, given that nitrites and nitrates present in vegetables, processed meats, and alcoholic beverages can undergo nitrosation reactions under specific conditions. The excessive use of synthetic preservatives may heighten this risk, suggesting a vital need for balance between preservation and safety.

While plant-based foods provide high concentrations of nitrates, they also contain significant amounts of antioxidants that inhibit nitrosation reactions and, consequently, the formation of nitrosamines. Therefore, based on current evidence, there is no valid justification for restricting their consumption. In contrast, processed meat products containing nitrites should be consumed with moderation.

Finally, from an analytical perspective, the findings confirm that conventional methods, such as High-Performance Liquid Chromatography (HPLC), may be insufficient for the precise detection of nitrosamines at trace levels. In this context, the implementation of more advanced techniques, such as Ultra-Performance Liquid Chromatography coupled with Tandem Mass Spectrometry (UPLC-MS/MS), offers superior sensitivity, selectivity, and reliability. This technological advancement strengthens quality controls and contributes significantly to the protection of public health.

Collectively, these results emphasize the importance of maintaining rigorous regulatory oversight, applying advanced analytical methodologies, and conducting continuous risk evaluations across both the pharmaceutical and food industries.

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