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Evolution of nitrosamine regulations: Lessons from pharmaceuticals applied to food safety management

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Abstract
Nitrosamines have emerged as a critical global concern in both pharmaceutical manufacturing and food safety due to their carcinogenic and genotoxic potential. This article examines the evolution of regulatory frameworks designed to control nitrosamine contamination, highlighting lessons learned from the pharmaceutical sector and their relevance to food safety management. The review outlines key contamination incidents that triggered regulatory responses, explores the role of advanced analytical techniques in detection, and evaluates the development of international guidelines by bodies such as the EMA, FDA, and WHO. Furthermore, the analysis emphasizes cross-sector differences in regulatory philosophy, acceptable intake thresholds, and incident response mechanisms, while also underscoring the opportunities for harmonization. By integrating Good Manufacturing Practices (GMP) from pharmaceuticals with Hazard Analysis and Critical Control Points (HACCP) in food systems, the paper argues for a unified framework to strengthen public health protection. Future directions call for global alignment of standards, investment in sensitive detection methods, and bridging research gaps concerning chronic exposure and interaction effects. This integrated approach can ensure more consistent, transparent, and science-driven management of nitrosamine risks across industries.

Keywords: Nitrosamines, pharmaceuticals, food safety, regulatory frameworks, contamination control, GMP, HACCP, analytical detection, global harmonization, public health

Introduction

Background on Nitrosamines

Nitrosamines are a wide range of nitrogen-based chemical compounds identifiable by the –N–N=O functional group (Aishwarya *et al*., 2025) [1]. These compounds are generally produced when secondary or tertiary amines react with nitrosating agents, most commonly nitrite ions, in acidic or oxidative environments. Although they were first identified in the late 1800s, it was not until the mid-1900s that they attracted significant toxicological and regulatory scrutiny, as research began to reveal their strong carcinogenic effects in laboratory animals (Vikram *et al*., 2023) [36]. Nitrosamines are contaminants found in various settings, including industrial operations, pharmaceuticals, cosmetics, and food supply chains. Their occurrence is typically unintentional, arising as a byproduct of manufacturing, processing, or storage conditions that allow nitrosation reactions to occur (Witkowska *et al*., 2022) [38].

The range of nitrosamines spans from straightforward compounds, such as N-nitrosodimethylamine (NDMA), to more intricate aromatic derivatives. Despite this diversity, many of them exhibit similar toxicological characteristics and mechanisms of action. As nitrosamines are typically not intentionally added, their presence often indicates failures in manufacturing controls or unintended chemical reactions within a product's composition (Tsuji *et al*., 2024) [35]. The current public health challenge involves not only detecting and measuring nitrosamines but also preventing their formation in both pharmaceutical and food products.

Formation Mechanisms in Pharmaceuticals and Food

In Pharmaceuticals

Nitrosamine contamination in pharmaceuticals arises through several well-defined pathways, typically involving reactions between amine-containing drug substances or intermediates and unintended nitrosating agents.

- **Residual nitrites:** Trace nitrites in raw materials, reagents, solvents, or water can react with secondary or tertiary amines in APIs or intermediates under specific pH and temperature conditions (Hao *et al*., 2024) [14].
- **Degradation during storage:** APIs or excipients with amine groups may undergo slow nitrosation when stored in warm, humid environments or in packaging that leaches nitrites (Ponting *et al*., 2022) [24].
- **Contaminated recovery solvents:** Improper solvent recycling in multipurpose facilities can lead to cross-contamination, particularly for nitrosamine-prone products (L. Zhang *et al*., 2024) [41].
- **Synthesis-related formation:** Certain synthetic routes involving amides, carbamates, or amine intermediates may yield nitrosamines when nitrosating agents are present, even at very low levels (Yu *et al*., 2017) [40].

Concerns intensified after the 2018 valsartan case, where NDMA and related nitrosamines were traced to a manufacturing change involving sodium nitrite under acidic conditions in the presence of secondary amines.

In Food

Nitrosamine formation in food follows similar chemical principles but is driven by sector-specific processing conditions and environmental sources.

- **Cured and processed meats:** Sodium nitrite used in preservation can react with naturally occurring amines during high-temperature cooking, forming volatile nitrosamines (Deveci & Tek, 2023) [9].

- **Beer and malt products:** Malting, drying, and open-flame kilning promote the formation of N-nitrosopyrrolidine and other volatile nitrosamines (Rani & Bhardwaj, 2021) [25].
- **Dairy products:** Contamination may result from nitrite-containing sanitizers or nitrite-rich animal feed.
- **Vegetables and drinking water:** Vegetables accumulate nitrate, which can be microbially reduced to nitrite during storage or digestion, enabling *in vivo* nitrosation.
- **Packaging migration:** Packaging materials containing amine-based additives may contribute to nitrosamine formation under certain storage conditions.

Although the underlying nitrosation chemistry is similar across both industries, effective control requires detailed understanding of their distinct processing environments and contamination pathways.

Health risks

Nitrosamines are among the most thoroughly studied chemical carcinogens, with consistent toxicological profiles across the class but considerable variation in potency.

- **Carcinogenicity:** IARC classifies many nitrosamines as Group 2A or 2B carcinogens. NDMA, in particular, is a Group 2A agent. Animal studies show tumor formation in organs such as the liver, lungs, kidneys, and gastrointestinal tract (Li & Hecht, 2022) [20].
- **Genotoxicity:** Nitrosamines undergo P450-mediated metabolic activation, producing alkylating intermediates that form DNA adducts and induce mutations, chromosomal damage, and genomic instability (Fahrer & Christmann, 2023) [12].
- **Toxicokinetics:** After ingestion or inhalation, nitrosamines are rapidly absorbed and distributed. Their short-lived but highly reactive metabolites act as potent initiators of DNA damage (Totsuka *et al*., 2020) [34].
- **Human epidemiology:** Although direct evidence is limited, occupational studies—especially in rubber manufacturing—and dietary exposure assessments link nitrosamine intake to increased cancer risks, particularly of the stomach, liver, and oesophagus.

Given their strong genotoxicity and lack of a clear safe threshold, regulatory agencies apply the ALARA (As Low as Reasonably Achievable) principle when setting exposure limits.

Regulatory Significance

Regulatory bodies focus on nitrosamines because of their significant toxicity, widespread potential for their presence, and the fact that they are rarely added on purpose. Despite the strict safety standards followed by both pharmaceuticals and food products, nitrosamine contamination presents a challenge to conventional quality control methods because of the following reasons:

- **Trace-level potency**: Owing to their significant cancer-causing potential, nitrosamines are subject to regulatory limits that are typically set in the low parts-per-billion (ppb) range.
- **Analytical complexity**: To identify nitrosamines at such minute levels, it is essential to employ methods that are both highly sensitive and selective, which, in turn, require specialized laboratory facilities.
- **Public trust**: Incidents of contamination can erode trust in regulatory bodies, industry standards, and product safety.

Regulatory organizations, such as the U.S. The Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) have established rigorous guidelines for managing nitrosamines in pharmaceuticals, usually defining compound-specific acceptable intake (AI) limits. In the food industry, standards are typically set for particular products identified as high-risk, such as cured meats, and are often supported by good manufacturing practices (GMP) and hazard analysis and critical control point (HACCP) systems (HACCP) (Bhirud *et al*., 2024) [6].

Increased global attention to nitrosamines has been sparked by several notable contamination incidents:

- **Pharmaceutical recalls (2018–present):** The discovery of NDMA and similar nitrosamines in ARBs, ranitidine, and metformin led to global recalls and unprecedented collaborations among regulatory bodies (Bharate, 2021) [5].
- **Food safety alerts**: Public alerts and import limitations have been issued due to high nitrosamine concentrations in processed meats, beer, and some dairy products.
- **International ripple effects**: These events have shown that the supply chains for both medicines and food are interconnected on a global scale, indicating that contamination problems in one area can have worldwide effects.

The outcome has been the merging of regulatory approaches that emphasize proactive risk evaluation, enhanced monitoring, and swift response strategies.

Rationale for Cross-Sector Learning

Shared Chemical Risk Profile

The basic chemistry involved in the formation of nitrosamines is similar in both the pharmaceutical and food industries. Both fields deal with secondary or tertiary amines, nitrosating agents, and conditions that can lead to undesirable side reactions. This common risk profile presents an opportunity to share knowledge between the two sectors.

Pharmaceutical Lessons for Food Safety

The swift action taken by the pharmaceutical sector in response to the valsartan crisis demonstrates how an effective regulatory system can harness scientific, industrial, and regulatory resources to address an emerging threat. Important lessons that can be applied elsewhere include the following:

- Proactive risk identification through systematic process evaluation.
- Achieving global standardization of analytical techniques to maintain uniform detection capability.
- Application of permissible intake thresholds based on toxicological risk evaluation.
- Applying lifecycle management strategies ensures oversight of product quality from the initial raw material stage to the final product.

Potential Benefits to Food Regulation

Incorporating aspects of the pharmaceutical regulatory framework, such as compulsory risk evaluations, standardized analytical methods, and enhanced post-market monitoring, could improve food safety systems in managing nitrosamine hazards. Additionally, applying quality-by-design (QbD) concepts from the pharmaceutical industry to HACCP-based food safety strategies may lead to more effective preventive measures.

Literature Review

Although nitrosamines have long been acknowledged as strong mutagenic carcinogens, their regulatory significance surged after 2018. This was due to the recall of several active pharmaceutical ingredients (APIs) and finished products contaminated with N-nitrosodimethylamine (NDMA) and similar compounds (Parr *et al*., 2019; Sedlo *et al*., 2021). For angiotensin II receptor blockers, commonly referred to as "sartans," the underlying issues were traced back to nitrosating conditions during the synthesis of the tetrazole ring, the use of sodium nitrite, and the presence of solvents such as DMF and NMP. These solvents break down into dimethylamine, which then undergoes nitrosation to produce NDMA (EMA 2020; Ray *et al*. 2020; Wichitnithad *et al*. 2023). A similar situation was observed with ranitidine, where NDMA formation was linked to instability under specific storage and temperature conditions (FDA, 2021; White, 2021). These events have led to a worldwide regulatory shift towards stricter guidelines, improved analytical standards, and systematic monitoring of nitrosamine impurities (FDA, 2024b; EMA, 2024).

In the pharmaceutical industry, the transition was supported by frameworks such as ICH M7, which outlined guidelines for evaluating and managing mutagenic impurities and set acceptable intake (AI) limits based on their carcinogenic potential (ICH, 2017; FDA, 2024a). The U.S. The FDA subsequently issued comprehensive guidance detailing risk assessments, confirmatory testing using advanced chromatographic and mass spectrometric methods, and established clear AI limits for both traditional nitrosamines and nitrosamine drug substance-related impurities (NDSRIs) (FDA, 2024b; FDA, 2024c). Similarly, the EMA adopted a comparable strategy, releasing opinions and technical guidelines that required marketing authorization holders to identify potential nitrosamine sources, prevent their formation, and conduct testing throughout the product lifecycle (EMA, 2024). Analytical capabilities have also advanced swiftly, with regulators recommending LC-MS/MS, GC-MS, and HRMS methods validated to detect nitrosamines at low ppb levels, ensuring consistent and comparable results across different laboratories (Sedlo *et al*., 2021; EMA, 2024).

Historically, food safety regulations have addressed nitrosamines by indirectly managing their precursors and the conditions that lead to their formation. Nitrosamines are formed in food when amines react with nitrosating agents, such as nitrite, during processing, cooking, or storage. Common sources include cured meats, smoked fish, beer, and malt-based products, where factors such as temperature, pH, and residual nitrite levels are critical. The Codex Alimentarius General Standard for Food Additives (GSFA) sets the maximum permissible levels for nitrites in specific food categories, often expressed as residual nitrite ions (GSFA, n.d.). In 2023, the European Food Safety Authority (EFSA) assessed a group of ten carcinogenic nitrosamines (TCNAs) and concluded that dietary exposure might pose health risks to EU consumers. They advised collecting more data on their presence and implementing strategies to mitigate risks in high-risk items, such as processed meats (EFSA, 2023; EFSA News, 2023; Eisenbrand *et al*., 2024).

The experience gained from pharmaceutical regulations provides valuable insights that can be applied to food safety management. One key lesson is the shift towards potency-based, compound-specific limits instead of general maximum use levels for precursors, a method already adopted in EFSA's TCNAs assessment. Another important concept is lifecycle risk management, which involves tracking and controlling potential nitrosamine sources from raw materials to processing, packaging, and storage. This is similar to how pharmaceutical companies oversee solvents, reagents, catalysts, and environmental conditions (FDA, 2024b; EMA, 2024). Implementing this within a HACCP framework would require explicit recognition of nitrosation chemistry as a hazard and incorporation of supplier qualification, process monitoring, and change-control protocols into food safety plans.

Another area where the pharmaceutical industry could enhance food sector control is through analytical harmonization. The swift implementation of validated high-sensitivity techniques in pharmaceuticals has ensured consistent and comparable results, facilitating coordinated recalls and regulatory measures. The EFSA has pointed out that variability in analytical methods and gaps in occurrence data pose challenges for effective food regulation (EFSA, 2023). By standardizing method performance criteria, such as detection limits and recovery rates, surveillance quality can be improved, leading to more robust risk assessments.

In conclusion, the strategies used for incident management and communication in the pharmaceutical industry can be applied to enhance food safety. Pharmaceutical organizations have coordinated efforts on a global scale, offering quantified risk assessments to provide context for their findings, and have communicated both the risks and the measures to mitigate them with transparency to uphold public trust (EMA 2020). Implementing similar approaches in the food industry could enhance public comprehension, decrease misinformation, and ensure that mitigation efforts are concentrated on processes and products that pose the highest risk.

Historical Evolution of Nitrosamine Regulation in Pharmaceuticals

1. Early Awareness and Initial Studies

Before the 2000s, nitrosamines were already recognized as a public health concern, although the full complexity of the issue was still emerging. Research from the 1950s and 1960s showed that secondary and tertiary amines react with nitrite in acidic conditions to produce N-nitrosamines,

several of which—such as NDMA and NDEA—proved to be potent liver carcinogens in animals. By the 1970s, rodent studies confirmed that even low, chronic exposures could induce tumors in multiple organs, establishing nitrosamines as exceptionally strong environmental carcinogens (Vikram *et al*., 2023) [36].

Seminal work by Druckrey and Preussmann in Germany and by Magee and Barnes in the UK clarified dose–response relationships, latency periods, and metabolic activation pathways, showing that cytochrome P450-mediated α-hydroxylation generates DNA-alkylating intermediates (Roje *et al*., 2024) [26]. This mechanistic insight linked chemical structure to carcinogenic potential and supported the classification of many nitrosamines as probable or known human carcinogens (Hecht, 1997) [15]. Through the 1980s and 1990s, genotoxic assays such as the Ames and micronucleus tests reinforced that nitrosamines act primarily through a DNA-reactive mode of action, making safe exposure thresholds unlikely.

Early research focused on nitrosamines in foods such as cured meats, beer, and smoked fish, but occupational studies soon expanded the concern, revealing elevated nitrosamine biomarkers among rubber industry workers and individuals exposed to nitrosated pesticides (Gough *et al*., 1978) [13]. This broadened understanding later proved essential when nitrosamines were detected as trace contaminants in pharmaceuticals.

Advances in analytical chemistry during the 1990s—particularly GC-TEA and GC-MS—enabled detection at parts-per-billion levels, revealing geographic and dietary differences in exposure (Dhorajiya *et al*., 2024; Tayel *et al*., 2025) [10, 32]. Toxicological reviews from this period consistently ranked NDMA among the most potent carcinogens studied, and IARC designated several nitrosamines as Group 2A/2B carcinogens. Regulatory bodies began proposing guideline values for food and drinking water, with North American agencies recommending nanogram-per-liter limits corresponding to lifetime cancer-risk estimates (Pepakayala *et al*., 2025) [22].

Pharmaceutical literature prior to 2000 acknowledged that drugs containing amines could form nitrosamines under certain storage conditions, although these findings were mostly theoretical, and pharmacopeias did not require nitrosamine testing (Vogel *et al*., 2025) [37].

By the late 1990s, food safety agencies in Europe, North America, and parts of Asia incorporated nitrosamine surveillance into risk-management systems, using measures such as nitrite control, optimized processing temperatures, and ascorbic acid inhibitors—efforts that successfully reduced dietary exposure (Vikram *et al*., 2023) [36].

Overall, pre-2000 research clarified nitrosamine formation mechanisms, carcinogenicity, and major exposure sources, laying the analytical and regulatory foundations that later became crucial when pharmaceutical contamination cases emerged.

2. Major Incidents Triggering Regulatory Action

The global concern over nitrosamine contamination in pharmaceuticals began in 2018 when NDMA was detected in valsartan, a widely used antihypertensive drug. The impurity originated from a manufacturing process change at Zhejiang Huahai Pharmaceutical, where the reaction of dimethylformamide and sodium nitrite under acidic conditions unintentionally produced nitrosamines (Charoo *et al*., 2023) [8]. European authorities first identified the issue, triggering worldwide recalls and revealing a broader vulnerability: modifications in API synthesis can generate genotoxic impurities if risks are not systematically evaluated (Tiwari *et al*., 2024) [33].

By 2019, NDMA and NDEA were also found in other angiotensin II receptor blockers, including losartan and irbesartan (Perkins *et al*., 2024) [23]. Investigations attributed these impurities to cross-contamination in shared equipment and unrecognized side reactions during intermediate steps, underscoring weaknesses in global supply chains and the need for transparency between manufacturers and marketing authorization holders.

The same year, NDMA contamination was detected in ranitidine, but unlike ARBs, the impurity originated from the drug's inherent instability. Studies demonstrated that ranitidine can break down to form NDMA during storage, especially at elevated temperatures. This shifted regulatory attention toward degradation-related nitrosamine formation, leading to complete recalls and demands for predictive stability testing (Tiwari *et al*., 2024) [33].

In 2020, low-level nitrosamines were identified in metformin and rifampicin, highlighting that the risk extends across therapeutic classes and is not limited to specific synthesis routes (Vikram *et al*., 2023) [36]. In response, the FDA and EMA issued directives (Shaik *et al*., 2020) [31] requiring:

- comprehensive nitrosamine risk assessments for all marketed and pipeline products;
- evaluation of synthetic routes, raw materials, reagents, and solvents;
- assessment of potential degradation pathways;
- use of advanced analytical tools such as LC-HRMS and GC-MS for detection.

The valsartan crisis marked a shift from reactive recalls to proactive prevention. Regulators now emphasize integrating nitrosamine control into early process design and maintaining rigorous oversight throughout increasingly complex supply chains.

These incidents also provide insight for food safety, as both industries face nitrosamine formation from similar chemical precursors under specific conditions. The pharmaceutical sector's approach—root-cause identification, process optimization, and robust analytical monitoring—offers a model for proactive contamination control in food production.

3. Development of Regulatory Guidelines

The discovery of nitrosamine impurities in pharmaceuticals prompted rapid regulatory action worldwide. Following the 2018 valsartan incident, the European Medicines Agency (EMA) issued early guidance urging manufacturers to review API synthesis routes and evaluate the potential for nitrosamine formation (Ruepp *et al*., 2021) [27]. By September 2019, the EMA formalized a three-step framework requiring:

- risk evaluation of all chemical and biological medicinal products,
- confirmatory testing where risks were identified, and
- implementation of corrective actions to eliminate or control nitrosamine formation.

Deadlines were established—generally 6–12 months for risk assessments, followed by time for mitigation efforts, with

priority given to high-risk APIs. These requirements were integrated into ICH M7(R1) guidance on mutagenic impurities, harmonizing approaches across major regulatory regions (Bhirud *et al*., 2024) [6].

The U.S. FDA followed a similar path, issuing its 2020 guidance, *Control of Nitrosamine Impurities in Human Drugs*. It emphasized science-based evaluation of nitrosamine risks across the drug lifecycle—including API synthesis, finished product manufacturing, and storage. The FDA also introduced acceptable intake limits for key nitrosamines (e.g., NDMA, NDEA, NMBA), expressed in nanograms per day and based on lifetime cancer risk (Shaik *et al*., 2020) [31]. The agency required manufacturers to employ sensitive analytical techniques such as validated LC-HRMS or GC-MS methods, offering detailed protocols to support implementation (Chang *et al*., 2020) [7].

The World Health Organization (WHO) similarly acknowledged the global significance of the issue. Through its Prequalification Program, WHO issued alerts and technical guidelines to support low- and middle-income countries in aligning their controls with EMA and FDA expectations (Charoo *et al*., 2023) [8]. WHO placed particular emphasis on prioritizing high-risk or essential medicines where contamination would have the greatest public health impact.

Across these bodies, risk assessment has become central to managing nitrosamine contamination. Manufacturers are expected to evaluate all plausible formation pathways, including deliberate nitrosating conditions and unintended interactions such as amine-containing excipients reacting with nitrites under heat or moisture (Vikram *et al*., 2023) [36]. Key considerations include:

- amine functionalities in APIs or intermediates,
- nitrite contamination in raw materials or water,
- process parameters (pH, temperature, solvents) that promote nitrosation, and
- degradation pathways linked to packaging or storage.

Mitigation strategies may involve modifying synthetic routes, improving raw material quality, adding scavengers, or adjusting storage conditions (Aishwarya *et al*., 2025) [1]. Regulators require that these assessments be thoroughly documented and periodically updated as part of Good Manufacturing Practice (GMP).

By 2021, both EMA and FDA had shifted from reactive management to proactive prevention, embedding nitrosamine control into the quality-by-design (QbD) framework. This transition ensures that risk identification and mitigation are integral to product lifecycle management and offers a template for similar contamination-control strategies in the food sector (Kao *et al*., 2022) [16].

4. Analytical Method Innovations

Recent advancements in analytical technologies have been central to controlling nitrosamine contamination, as highly sensitive and reliable detection methods are essential for meeting regulatory expectations. Early spectrophotometric techniques lacked the sensitivity needed to detect trace nitrosamines, especially in complex pharmaceutical matrices. With rising regulatory scrutiny, detection strategies shifted toward advanced chromatographic–mass spectrometric tools, particularly LC–MS/MS and GC–MS (Witkowska *et al*., 2022) [38].

LC–MS/MS rapidly became the preferred platform because of its exceptional selectivity, suitability for thermally unstable analytes, and compatibility with aqueous-based mobile phases. Modern triple-quadrupole systems can quantify nitrosamines below parts-per-billion levels, exceeding EMA, FDA, and WHO expectations (Dhorajiya *et al*., 2024) [10]. Improvements in ionization efficiency, chromatographic separation, and interference reduction—along with complementary high-resolution mass spectrometry (HRMS)—have strengthened analytical reliability and structural confirmation.

GC–MS remains indispensable for volatile nitrosamines such as NDMA and NDEA. Using selective ion monitoring or MS/MS modes, GC–MS achieves detection limits comparable to LC–MS/MS (Wu *et al*., 2008) [39]. Techniques such as automated thermal desorption and SPME have enhanced sample throughput and simplified preparation. In certain cases, GC–MS is preferred because of its superior ability to isolate volatile impurities from excipient-rich formulations (Selaya *et al*., 2024) [29].

Recent trends emphasize surpassing regulatory sensitivity requirements. Isotope-dilution approaches, using isotopically labeled internal standards, now enable precise quantification by minimizing matrix effects. Sample preparation enhancements—including SPE and DLLME—improve analyte recovery and reduce interference from APIs and excipients. Laboratories increasingly use orthogonal methods to cross-validate results from LC–MS/MS and GC–MS, reducing the risk of false positives or negatives (Liu *et al*., 2021) [21].

Pharmaceutical innovations have also migrated into food safety, where similar challenges exist in detecting nitrosamines in processed meats, dairy products, and fermented foods. Regulators encourage methodological alignment across sectors, acknowledging that shared technologies can support both pharmaceutical and food surveillance with appropriate modifications to sample preparation.

Currently, the field is moving toward integrated analytical platforms capable of simultaneously screening multiple contaminants. This aligns with the shift toward preventive quality control, where ultra-sensitive analytical methods serve both regulatory compliance and proactive risk management. As detection limits continue to improve, these techniques will play a critical role in safeguarding public health and guiding rapid, evidence-based regulatory responses.

5. Integration into GMP & ICH Guidelines

The integration of nitrosamine control measures into existing Good Manufacturing Practice (GMP) systems and International Council for Harmonisation (ICH) guidelines has played a pivotal role in formalizing risk reduction across the pharmaceutical industry. Although ICH M7—focused on managing DNA-reactive (mutagenic) impurities—and ICH Q3D—addressing elemental impurities—were not originally designed with nitrosamines in mind, their core principles have been adapted in response to recent contamination crises (Amberg *et al*., 2016) [2].

ICH M7 provides a structured approach for identifying, evaluating, and controlling mutagenic impurities through risk-based acceptable intake (AI) limits derived from lifetime cancer-risk models. Given the potent genotoxicity of nitrosamines, these impurities were incorporated into the

M7 framework after the 2018 valsartan crisis, leading to extremely low permissible daily exposure (PDE) limits—often in the nanogram range (Amberg *et al*., 2018) [3]. M7's emphasis on structural alerts, impurity identification, and toxicological qualification has become central to nitrosamine control strategies.

Although ICH Q3D primarily targets elemental impurities, its methodical risk-assessment approach has indirectly strengthened nitrosamine management. Q3D's focus on evaluating contamination sources—including raw materials, equipment, water systems, and packaging—parallels the comprehensive mapping required to understand nitrosamine formation pathways. Its emphasis on supply-chain control also aligns with the need to prevent cross-contamination and ensure raw material purity (Charoo *et al*., 2023) [8].

Incorporating nitrosamine oversight into GMP systems required a shift from reactive to proactive quality management. Regulators now mandate retrospective risk assessments for all marketed products, identification of potential nitrosamine-forming pathways, and the adoption of preventive measures such as process redesign, raw-material qualification, and enhanced supplier oversight. This aligns with GMP's fundamental "quality by design" philosophy rather than "quality by testing" (Azeeze *et al*., 2023) [4]. Batch release increasingly depends on validated analytical data, signaling stronger alignment between GMP documentation and ICH impurity guidelines (Doneski & Dong, 2023) [11].

A major outcome of this integration is global regulatory harmonization. Agencies such as the EMA, FDA, and Health Canada have issued nitrosamine-specific guidelines that explicitly reference ICH M7 principles, providing consistency in toxicological evaluation and acceptable-intake calculations (Ruepp *et al*., 2021) [27]. This harmonization reduces uncertainty for multinational manufacturers and promotes standardized control strategies across regulatory jurisdictions.

Overall, the incorporation of nitrosamine considerations into GMP and ICH frameworks has substantially improved the industry's ability to manage genotoxic impurities. It has also established a robust foundation for addressing emerging contaminants—both in pharmaceuticals and in sectors such as food safety—where similar principles of hazard identification, exposure assessment, and process control are essential for preventing contamination by high-risk chemical species.

Nitrosamine Control in Food Safety Regulatory

Over the years, regulations concerning nitrosamine control in food safety have undergone significant changes, primarily due to increasing evidence of their carcinogenic potential and widespread presence in the food supply. These compounds are mainly generated through chemical reactions between nitrosating agents, such as nitrite, and secondary or tertiary amines, and can be formed at different stages of food production, processing, and storage.

1. Sources in Food

Food processing is a major contributor to nitrosamine exposure because nitrites and nitrates—widely used as curing agents—can react with amines during heating. In cured meats such as bacon, ham, and sausages, nitrites combine with secondary amines during cooking, with higher levels formed during high-temperature processes like frying and grilling. Similar nitrosation reactions occur in beer brewing, fish preservation, and cheese fermentation, where residual nitrites interact with amine-containing compounds under acidic or thermal conditions (Seo *et al*., 2022) [30].

Food packaging can also introduce nitrosamines. Certain rubber-based elastomers used in bottle caps, jar seals, and food-handling gloves may leach small amounts of nitrosamines into products—particularly beverages (Deveci & Tek, 2023) [9]. In addition, some inks and adhesives contain amine precursors that can react with atmospheric nitrogen oxides during storage, forming nitrosamines on package surfaces.

Environmental pathways contribute further. Crops grown in nitrate-rich soil or irrigated with contaminated water—often due to excessive fertilizer use—can accumulate nitrosamine precursors (Scanlan & Issenberg, 1975) [28]. These precursors may convert into nitrosamines during processing or cooking. Industrial emissions and tobacco smoke in storage environments also introduce nitrogen oxides capable of triggering surface nitrosation reactions in susceptible foods.

Thermal processing methods such as roasting, smoking, and drying provide conditions that facilitate nitrosamine formation (Koszucka & Nowak, 2018) [17]. For example, roasting malt in beer production or smoking fish and meats exposes foods to nitrogen oxide–rich smoke that promotes nitrosation. Coffee roasting has also been associated with nitrosamine and PAH formation, though typically at lower levels than those found in meat products.

Effective nitrosamine control in food requires a comprehensive regulatory approach: reducing precursor levels in raw materials, optimizing processing conditions, limiting chemical migration from packaging, and managing nitrogen oxide exposure in production and storage environments (Y. Zhang *et al*., 2021) [42]. Lessons from pharmaceutical regulation emphasize the importance of evaluating all potential contamination routes.

By understanding how precursors, processing, and environmental conditions interact, regulators can establish unified standards for acceptable nitrosamine levels and promote preventive strategies across the food supply chain—mirroring the proactive quality-control practices adopted by the pharmaceutical industry after major contamination events.

2. Current Regulatory Standards

Current regulations on nitrosamines in food and pharmaceuticals reflect a coordinated yet regionally adapted approach shaped by global bodies, national agencies, and sector-specific authorities. At the international level, the Codex Alimentarius Commission—jointly developed by FAO and WHO—provides overarching food safety standards, including guidance on nitrosamine contaminants (Lawrence *et al*., 2024) [19]. Although Codex does not prescribe universal maximum residue limits for all nitrosamines, it recommends acceptable levels for high-risk categories such as cured meats and certain processed fish products, supporting regulatory harmonization across member countries.

In the European Union, nitrosamine oversight is divided between the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) (Lampen *et al*., 2024) [18]. EFSA assesses dietary exposure, evaluates toxicological risks, and proposes maximum permissible

concentrations—typically in the low microgram-per-kilogram range. The EMA, in contrast, enforces stringent controls in the pharmaceutical sector, requiring manufacturers to identify potential nitrosamine-forming pathways, apply validated analytical methods, and implement corrective actions when impurities are detected.

The U.S. Food and Drug Administration (FDA) also regulates nitrosamines in both industries. For pharmaceuticals, the FDA sets extremely low acceptable intake limits—at parts-per-billion levels—based on lifetime cancer risk models. In food, the agency monitors high-risk items such as smoked meats, beer, and certain cheeses, issues action levels, and encourages industry measures that reduce nitrosamine precursors during processing (Bharate, 2021) [5].

Other regulatory bodies, including Health Canada, Japan's Ministry of Health, Labour and Welfare, and the Australia–New Zealand Food Standards Code, have implemented similar risk-based limits tailored to local dietary patterns, industrial processes, and environmental conditions. Collectively, these frameworks underscore a shift toward preventive, science-driven control strategies and reflect growing alignment between food and pharmaceutical regulations, informed by lessons learned from contamination events (Lampen *et al*., 2024) [18].

3. Analytical Challenges in Food Matrices

The analysis of nitrosamines in food matrices is challenging because of the intricate and varied compositions of food. Numerous food items, including cured meats, fermented goods, dairy products, and beverages, contain proteins, fats, sugars, and natural pigments that can interfere with the detection and quantification of trace contaminants. These components within the matrix may lead to signal suppression or enhancement in analytical instruments, resulting in inaccurate readings if sample preparation is not properly conducted.

Another major issue is the chemical instability of certain nitrosamine types, which can break down or change during storage, extraction or concentration processes. Fluctuations in moisture levels, pH, and the presence of reactive substances in food can also affect the recovery rates and detection thresholds. Moreover, some processing and cooking techniques can produce new nitrosamines after production, making it difficult to retrospectively assess contamination.

To tackle these challenges, analysts frequently employ highly sensitive and selective techniques, such as gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–tandem mass spectrometry (LC-MS/MS), along with thorough sample preparation methods, such as solid-phase extraction. Nevertheless, the necessity to customize extraction and calibration techniques for each food type makes large-scale monitoring resource-demanding. These analytical complexities underscore the significance of standardized protocols and ongoing method validation to ensure reliable nitrosamine monitoring across various food products.

Cross- Sector Comparative Analysis

1. Regulatory Philosophy and Risk Tolerance

Table 1: Comparative Regulatory Philosophy and Risk Tolerance for Nitrosamines

Regulatory Body	Sector	Metric Used	Typical Limit / Approach	Notes
FDA	Pharmaceuticals	Acceptable Intake (AI, ng/day)	NDMA: 96 ng/day; NDEA: 26.5 ng/day; category-based defaults for NDSRIs (26.5 or 100 ng/day)	Compound-specific limits derived from carcinogenicity data; AI values aim to keep lifetime cancer risk ≤ 1 in 100,000
EMA	Pharmaceuticals	AI via Carcinogenic Potency Categorisation Approach (CPCA) or read-across	NDMA: 96 ng/day; NDEA: 26.5 ng/day; default AI for some NDSRIs = 18 ng/day	More conservative defaults for unknown potency; harmonization with ICH M7 principles
EFSA	Food	Margin of Exposure (MOE) from BMDL10 (µg/kg bw/day)	Uses BMDL10 = 10 µg/kg bw/day (from NDEA) and considers MOE ≥ 10,000 as low concern	No ADI set for genotoxic carcinogens; MOE is used for risk prioritization rather than setting legal limits
Codex Alimentarius	Food	Maximum Levels (MLs) for precursors or product-specific nitrosamine levels	No compound-specific ADIs; MLs for nitrite/nitrate in processed meat; occasional product MLs for volatile nitrosamines	Focuses on precursor control to prevent formation during processing/storage

2. Testing and Surveillance

Table 2: Pharma vs. Food

Aspect	Pharma	Food
Testing Frequency	Continuous, every batch.	Periodic, risk-based.
Triggers	Development, process changes, routine QC.	Routine sampling, incident-driven.
Methods	Ultra-sensitive LC-MS/MS, GC-MS (ng levels).	Codex/ISO methods, higher detection limits.
Oversight	Real-time, intensive regulatory review.	Scheduled or incident-based inspections.

Inference: In the pharmaceutical industry, nitrosamine testing is an integral part of an ongoing quality control process, with each batch subjected to highly sensitive analyses, such as LC-MS/MS or GC-MS, to identify trace impurities at nanogram concentrations. This relentless monitoring is motivated by strict regulatory demands and the high-risk nature of the pharmaceutical products. Conversely, food safety testing is conducted periodically and based on risk, where routine sampling and inspections are enhanced by specific checks in response to contamination alerts. Although food industry methods adhere to Codex Alimentarius or ISO standards, their

detection limits are typically higher than those in pharmaceuticals, reflecting differences in regulatory approaches, acceptable daily intake levels, and the extent of production supervision.

3. Incident Response Model

Table 3: Incident Response Models comparison

Aspect	Pharma	Food
Recalls	Immediate, full batch withdrawal.	Slower, often partial recalls.
Public Alerts	Frequent, detailed via regulators.	Brief consumer-focused notices.
Transparency	Full technical reports to regulators.	Limited technical data released.

Inference: In the pharmaceutical industry, responses to nitrosamine contamination are swift and strictly controlled, with entire batches recalled immediately upon confirmation of contamination. Regulatory bodies, such as the FDA and EMA, issue comprehensive alerts that frequently include technical information, testing limits, and analyses of root causes to ensure transparency.

Conversely, the food industry's reactions are typically more deliberate and focused, often involving the recall of only certain product lots instead of entire production runs. Public announcements are generally brief, aimed at consumers, and offer basic safety advice without delving into technical details. This distinction highlights the regulatory approach of each sector: pharmaceuticals emphasize the swift elimination of risks and scientific openness, whereas food safety strategies aim to balance public health concerns with the stability of the supply chain and market effects.

4. Stakeholder Engagement

Table: Stakeholder Engagement: Pharma vs. Food

Aspect	Pharma	Food
Industry Training	Frequent, mandatory GMP/nitrosamine training.	Periodic HACCP training; nitrosamine focus less consistent.
Public Communication	Detailed safety alerts with technical data.	Simplified consumer notices; minimal technical detail.
Research Collaboration	Strong academic/industry ties for toxicology & method validation.	Project-based collaborations, mainly applied food safety.

Pharmaceutical regulators mandate stringent and ongoing training on GMP and nitrosamine risk management, bolstered by strong collaborations between academia and industry for method development and toxicological research. Communication with the public is open and technically detailed, addressing both professionals and stakeholders alike. Conversely, the food industry employs more general HACCP-based training with less emphasis on nitrosamine specifics, depends more on research collaborations tailored to specific projects, and focuses on simplified public messaging aimed at reassuring consumers rather than providing technical details.

Methodology

1. Databases Utilized

A literature review was performed by accessing several well-regarded academic and regulatory databases to ensure a thorough examination of the pertinent publications. The main databases used were Web of Science, PubMed, Scopus, and ScienceDirect. Each was chosen for its particular strength in covering various fields: Web of Science for its extensive scholarly records, PubMed for studies in biomedical and toxicology, Scopus for research focused on regulatory and policy matters, and ScienceDirect for in-depth technical and applied science literature.

2. Search Strategy and Keywords

A comprehensive search approach was employed, utilizing both Boolean operators and controlled vocabulary, when applicable. The primary keywords and their combinations used were as follows:

- "Nitrosamine regulations"
- "Pharmaceutical contamination"
- "Food safety policy"
- "Risk assessment"

To encompass studies with different terminologies, additional synonymous and related terms, such as "nitrosamine limits," "GMP compliance," and "Codex standards" were included. The searches were conducted multiple times across various databases to reduce the likelihood of missing relevant information.

3. Inclusion and Exclusion Criteria

Studies and documents were included if they met the following criteria.

- **Inclusion:** Articles from peer-reviewed journals, official regulatory documents, guidelines, and technical reports released from 1990 to the present; these works focused on the regulation of nitrosamines, incidents of contamination, or risk management in pharmaceuticals or food products.

- **Exclusion:** Sources that have not undergone peer review, opinion articles lacking supporting evidence, publications before 1990, and studies that do not pertain to the regulatory framework or risk assessment processes of either sector.

4. Data Extraction and Synthesis

Relevant publications underwent a two-step screening process: an initial review of the titles and abstracts, followed by a comprehensive evaluation of the full text. Information gathered from each qualifying source included the following:

- Publication year and source
- Sector focus (pharmaceutical, food, or both)
- Geographic/regulatory jurisdiction
- Reported nitrosamine sources and risk assessment approaches
- Regulatory limits and compliance measures

- Case examples and lessons learned

The collected data were structured into a comparative analytical framework to assess the similarities and differences in nitrosamine regulation between the pharmaceutical and food industries. This framework facilitated a systematic cross-sector analysis of regulatory philosophies, testing and monitoring methods, incident response strategies and stakeholder involvement. The findings were qualitatively synthesized, and thematic coding was used to identify recurring patterns, regulatory gaps, and opportunities for integrating policies across sectors.

Challenges in Translating Pharms Lessons to Food

1. Complexity of Food Supply Chains

The global food supply chain is naturally more intricate than the controlled environment in which pharmaceuticals are manufactured. Unlike medicines, which are generally produced in centralized locations following strict Good Manufacturing Practices (GMP), food items often go through numerous stages of production, processing, packaging, distribution, and retail. Each of these stages presents the potential for nitrosamine formation, whether due to interactions between ingredients, environmental factors, or processing conditions such as high-temperature cooking or curing. This complexity makes it more challenging to trace the sources of contamination and complicates the implementation of control strategies similar to those used in the pharmaceutical industry.

2. Diverse Regulatory Authorities and Standards

In most regions, pharmaceutical regulations are managed by a central authority, such as the FDA in the United States or the EMA in the European Union, which allows for consistent enforcement. Conversely, food regulation is handled by a more extensive array of national, regional, and sometimes local agencies, each with distinct responsibilities, enforcement strategies, and resource availability. International organizations, such as Codex Alimentarius, offer guidance but lack the authority to enforce binding standards. This fragmented system leads to variations in acceptable limits, testing protocols, and compliance schedules, complicating the direct application of pharmaceutical nitrosamine standards in the pharmaceutical industry.

3. Cost and Infrastructure Barriers

Advanced methods for detecting and quantifying nitrosamines, such as LC-MS/MS and GC-MS, are well established in the pharmaceutical industry. However, they require substantial financial investment, specialized knowledge, and ongoing calibration. Many food testing laboratories, especially in developing areas, may not have the required infrastructure or skilled staff to perform high-sensitivity tests. Applying pharmaceutical-grade testing standards across the food industry, including small and medium-sized businesses, could result in significant financial burdens that may not be viable without subsidies or gradual implementation strategies.

4. Public Perception and Communication

When pharmaceutical products are recalled due to nitrosamine contamination, communication is typically technical and directed at healthcare professionals and regulatory authorities. In contrast, the food industry must communicate with a wider audience to address consumer concerns regarding safety, trust, and brand image. Messages that are too technical can lead to confusion, while overly simplified messages might lose credibility if important details are left out. The key challenge is to strike a balance between being transparent and clear, ensuring that risk messages are accurate and appropriate without causing unnecessary panic while still encouraging the right actions.

Future Direction

1. Framework for Unified Nitrosamine Control

One promising approach involves creating a comprehensive risk management framework that merges the stringent standards of pharmaceutical Good Manufacturing Practices (GMP) with the preventive strategies of Hazard Analysis and Critical Control Points (HACCP) from the food industry. GMP ensures thorough quality control from the acquisition of raw materials to the testing of the final product, whereas HACCP focuses on identifying hazards and implementing preventive measures at key stages in the production process. A unified framework could set cross-industry benchmarks for risk evaluation, contamination prevention, and corrective measures tailored to the unique manufacturing and supply chain characteristics of each sector. This integration would also promote shared training initiatives, uniform documentation practices and consistent verification procedures.

2. Global Regulatory Harmonization Efforts

Considering the international scope of both pharmaceutical and food supply chains, it is essential to harmonize nitrosamine standards to prevent fragmented compliance challenges and potential loopholes. Global entities, such as the World Health Organization (WHO) and Codex Alimentarius, could act as key platforms for standardizing acceptable daily intake limits, analytical testing criteria, and incident reporting procedures. Regulatory discussions, both bilateral and multilateral, akin to those conducted by the International Council for Harmonisation (ICH) in the pharmaceutical sector, should be expanded to incorporate food safety authorities. This would help ensure that the guidance documents and monitoring expectations gradually align.

3. Advances in Analytical Technologies

Advancements in nitrosamine control will be influenced by improvements in detection sensitivity, speed, and cost efficiency. The development of hybrid analytical platforms that integrate liquid chromatography–mass spectrometry (LC-MS/MS) with gas chromatography–mass spectrometry (GC-MS) could improve the accuracy of the results for both intricate drug formulations and diverse food matrices. Moreover, the use of portable, field-deployable sensors and compact analytical devices could enable real-time monitoring at various stages of the production process, thereby minimizing the delay between contamination and its detection.

4. **Research Gaps**

There are still considerable gaps in our knowledge regarding the long-term health effects of chronic exposure to low levels of nitrosamines, especially when this exposure is from various dietary and environmental sources. Research

on the interactions, whether synergistic or antagonistic, between nitrosamines and other components in food or drugs is limited but essential for improving risk-assessment models. Additionally, more information is required on the kinetics of nitrosamine formation during novel food processing technologies and innovative pharmaceutical manufacturing techniques. Bridging these gaps will require interdisciplinary collaboration among toxicologists, chemists, epidemiologists, and regulatory scientists, with the support of targeted research funding.

Conclusions

This review underscores the changing dynamics of nitrosamine regulation within the pharmaceutical and food industries, charting its progression from initial toxicological awareness to contemporary analytical and regulatory frameworks. The results indicate that insights gained from the pharmaceutical sector, especially in areas such as thorough risk evaluation, sophisticated analytical techniques, and open incident management, can provide valuable direction for enhancing nitrosamine control in food safety management. Although sector-specific variations exist in production methods, supply chains, and consumer interactions, the fundamental scientific and regulatory principles exhibit considerable overlap.

Key suggestions from this analysis include implementing a unified risk management framework that incorporates both Good Manufacturing Practices (GMP) and Hazard Analysis and Critical Control Points (HACCP) principles. It also emphasizes the need for global regulatory consistency regarding acceptable intake limits and testing standards, as well as ongoing investment in advanced analytical technologies for more sensitive, rapid, and cost-effective detection methods. Furthermore, addressing research gaps related to chronic low-level exposure and cross-contamination pathways is crucial for enhancing regulatory decisions in both sectors.

There is an evident necessity for cohesive policy formulation that brings together pharmaceutical and food safety regulators, industry participants, and research organizations under a unified approach to manage nitrosamine risks. By encouraging collaboration across sectors, standardizing monitoring techniques, and synchronizing communication strategies, regulatory authorities can enhance public health protection while simplifying compliance across industries. The merging of expertise from these two vital areas offers a distinct opportunity to create a thorough, science-based, and universally applicable framework for addressing nitrosamine risks in the future.

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