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# Review on Nitrosamine Impurities Present in Drugs and Medicines

**Prajwal S Adhav, Dr. Janhvi Rao, Prof. Sharvari Chavan**
Abhinav Education Society's College of Pharmacy (B.Pharm), Narhe, Pune, India

**Abstract:** *The detection of more than one nitrosamine impurity in pharmaceuticals, exceeding a total quantity of 26.5 ng/day based on the maximum daily dose (MDD), prompts the FDA to request manufacturers to contact the agency for evaluation. This review focuses on the presence of nitrosamine impurities in drugs and the importance of controlling potentially mutagenic impurities to assess carcinogenic risk in humans. The recent identification of nitrosamine impurities in various marketed pharmaceuticals has heightened interest in their mutagenic and carcinogenic potential. Nitrosamines belong to a 'cohort of concern,' meaning standard control protocols, such as the threshold of toxicological concern (TTC), are not applicable. Drugs such as sartans, ranitidine, and nizatidine have been found to contain these impurities, which often arise from the use of solvents, catalysts, and raw materials during the manufacturing process. Regulatory agencies have issued interim notices and press releases regarding the control of these impurities. Preventing nitrosamine impurities can be achieved by modifying the manufacturing process or implementing precautions during the production of drug substances and products. Validated analytical methods, including gas chromatography, mass spectrometry, and liquid chromatography, are used to identify and quantify these impurities. Nitrosamines typically form due to reactions between secondary and tertiary amines or ammonium salts and nitrosating agents. The European Medicines Agency (EMA) was the first to finalize guidelines on the presence of nitrosamine impurities in sartan medications.*

**Keywords:** Chromatography, medicine, nitrosating agent, European Medical Agency, Food and Drug Administration

## I. INTRODUCTION

Nitrosamines are a family of carcinogenic impurities formed by reactions of secondary amides, carbamates, amines, and derivatives of urea with nitrite and other nitrogenous agents, where nitrogen typically has a +3 oxidation state. These impurities can be introduced during the manufacturing and packaging processes of drugs. The presence of nitrosamines in pharmaceuticals has been a significant concern due to their mutagenic and carcinogenic properties.[1,2]

Common sources of nitrosamine contamination include solvents, catalysts, and raw materials used in drug production. Regulatory agencies such as the FDA and the European Medicines Agency (EMA) have identified and regulated several nitrosamines due to their potential health risks. General methods for detecting nitrosamine impurities include Headspace Gas Chromatography-Mass Spectrometry (HS-GC-MS) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS).[3]

The primary nitrosamines found in drugs include:

- NDMA: N-Nitrosodimethylamine
- NDEA: N-Nitrosodiethylamine
- NDIPA: N-Nitrosodiisopropylamine
- NEIPA: N-Nitrosoethylisopropylamine
- NDBA: N-Nitrosodi-n-butylamine
- NMEA: N-Nitrosomethylethylamine
- NDPA: N-Nitrosodi-n-propylamine
- NMBA: N-Nitroso-N-methyl-4-aminobutyric acid
- NPYR: N-Nitrosopyrrolidine

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- NPIP: N-Nitrosopiperidine[4]

In July 2018, the FDA and EMA announced the detection of carcinogenic impurities such as NDMA and NDEA in various drug products. These impurities were particularly found in angiotensin II receptor blockers (ARBs) or sartans, which are used to treat hypertension (high blood pressure) and heart failure. The investigation expanded in 2019 to include the detection of nitrosamine impurities in pioglitazone, a drug used to treat diabetes, and ranitidine, an H2 blocker used for stomach acidity. Additionally, low levels of nitrosamine impurities were found in metformin, a common diabetes medication, leading to further investigation by the FDA and EMA.[5,6]

## II. MATERIAL AND MANAGEMENT

Nitrosamine impurities can incorporate into drug products through various pathways, including the manufacturing process, cross-contamination, product degradation, direct introduction, and involvement of raw materials, intermediates, solvents, catalysts, chemicals, and reagents. Understanding these sources and implementing effective management strategies is crucial to minimizing nitrosamine contamination in pharmaceuticals.[6]

### Sources of Nitrosamine Impurities

**Manufacturing Process**:

- **Raw Materials and Intermediates**: Nitrosamines can form due to reactions involving carbamates, amides, N-alkyl amides, secondary or tertiary amines, and quaternary ammonium salts. The type, structure, and concentration of the nitrosating agent influence the extent of impurity formation, with secondary amides being particularly reactive.
- **Recovered Solvents and Catalysts**: Reusing solvents and catalysts treated with nitrites or nitric acid to destroy residual azides can lead to nitrosamine formation.
- **Decomposition**: Solvents and other materials can decompose during the manufacturing process, resulting in by-products like dimethylamine or diethylamide, which can form nitrosamines such as NDMA and NDEA.

**Cross-Contamination**:

- **Manufacturing Environment**: Cross-contamination can occur between different manufacturing processes or products made on the same production line, introducing nitrosamines into drug substances or products.

**Packaging Materials**:

- **Reactive Materials**: Certain packaging materials, such as lidding foils containing nitrocellulose or printing primers, can react with amines in printing inks to form nitrosamine impurities. These impurities can transfer to drug products.

**Vendor-Supplied Materials**:

- **Contaminated Raw Materials**: Starting materials or raw materials supplied by vendors may already contain nitrosamine impurities, which can be introduced into the drug product.

**Manufacturing Process Optimization**:

- **Inadequate Control**: Poorly controlled reaction conditions, such as inappropriate temperature, pH, or sequence of adding reagents, intermediates, or solvents, can lead to the formation of nitrosamine impurities.[7,8]

### Regulatory Guidelines

Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have provided guidelines to manage and mitigate the risk of nitrosamine contamination.

**European Medicines Agency (EMA)**:

The EMA has assessed the risk of nitrosamine formation and provided guidance to prevent contamination during the manufacture of human medicines. Notably, they identified nitrosamine contamination, including NDMA, in blood pressure drugs known as sartans in mid-2018. The EMA's guidelines focus on ensuring that manufacturers take appropriate measures to control and limit nitrosamine impurities in drug products.

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**Food and Drug Administration (FDA)**:
The FDA issued guidelines recommending that manufacturers complete a risk assessment for approved products and those on the market. This includes steps to reduce nitrosamine contamination within six months of guideline publication. The recommended time for completing the risk assessment was extended to March 31, 2021. Manufacturers must maintain risk assessment documents for review upon request.
The FDA's industry guideline, titled "Control of N-Nitrosamine Contamination in Human Drugs," outlines steps for detecting and preventing nitrosamine contamination in pharmaceutical products. This guideline emphasizes conditions that may lead to contamination and provides recommendations for mitigating these risks.[9,10]

**Strategies for Management**
**Risk Assessment**:
- Conduct comprehensive risk assessments to identify potential sources of nitrosamine impurities in the manufacturing process.

**Process Optimization**:
- Optimize manufacturing conditions, such as controlling temperature, pH, and the sequence of adding reagents, to minimize the formation of nitrosamines.

**Vendor Qualification**:
- Ensure that raw materials and intermediates from vendors are free from nitrosamine contamination through rigorous testing and qualification processes.

**Cross-Contamination Prevention**:
- Implement stringent cleaning and segregation procedures to prevent cross-contamination between different manufacturing processes.

**Analytical Testing**:
- Use validated analytical methods such as HS-GC-MS and LC-MS/MS to detect and quantify nitrosamine impurities in raw materials, intermediates, and finished products.

By understanding the various sources of nitrosamine impurities and adhering to regulatory guidelines, manufacturers can effectively manage and minimize the risk of nitrosamine contamination in drug products, ensuring patient safety and regulatory compliance.[11,12]

**Guidance for Marketing Authorization Holders**
Marketing authorization holders (MAHs) are responsible for ensuring the safety and quality of their pharmaceutical products. The European Medicines Agency (EMA) has provided detailed guidance to help MAHs prevent and mitigate the presence of nitrosamine impurities in human medicines. The key points of this guidance are outlined below:
**Review Production Processes**:
- MAHs should review their production processes to identify all products containing organic matter that may be susceptible to nitrosamine contamination.
- This review should focus on identifying potential sources of nitrosamines and assessing the risk of their presence in drug products.

**Regulatory Review and Guidance**:
- In June 2020, the EMA finalized a review under Article 5(3) of Regulation (EC) No 726/2004. This review provides guidance to market authorization holders on how to avoid the presence of nitrosamine contaminants in human medicines.
- The Committee for Medicinal Products for Human Use (CHMP) has requested that MAHs review all human chemical and biological drugs for the possible presence of nitrosamines and test products deemed at risk.

**Implement Control Strategies**:
- MAHs must implement appropriate control strategies to prevent or reduce the presence of nitrosamine pollutants. This may involve improving production processes, enhancing quality control measures, and ensuring thorough testing of raw materials and finished products.

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- Control strategies should be based on a thorough risk assessment and should be regularly updated to address new risks as they are identified.

**Ongoing Monitoring and Compliance**:

- MAHs should establish ongoing monitoring programs to detect nitrosamine impurities in their products. This includes regular testing and analysis of drug substances and products using validated analytical methods.
- MAHs must maintain compliance with regulatory requirements and guidelines, ensuring that their products meet safety and quality standards.[13,14]

**Additional Points on Nitrosamine Impurities in Drugs and Medicines**

**Potential Sources of Nitrosamine Contamination**

**Water Supply**:

- Contaminated water used during the manufacturing process can be a source of nitrosamine impurities. This contamination can occur if the water supply is treated with chloramines, which can react with organic compounds to form nitrosamines.

**Environmental Contaminants**:

- Nitrosamines can be present in the environment due to industrial activities and pollution. These environmental contaminants can enter the manufacturing facility and contaminate the drug substances or products.

**Storage Conditions**:

- Improper storage conditions, such as exposure to high temperatures and humidity, can lead to the degradation of drug products and the formation of nitrosamine impurities.

**Biological Pathways**:

- Certain biological processes can produce nitrosamines. For instance, the metabolic activation of some drugs within the human body can lead to the formation of nitrosamines as metabolites.[15]

**Analytical Methods for Detection**

**Gas Chromatography-Mass Spectrometry (GC-MS)**:

- This method is widely used for detecting volatile nitrosamines. It involves the separation of nitrosamines by gas chromatography, followed by their detection using mass spectrometry.

**Liquid Chromatography-Mass Spectrometry (LC-MS)**:

- LC-MS is used for detecting non-volatile and thermally labile nitrosamines. It combines liquid chromatography's separation capabilities with mass spectrometry's detection sensitivity.

**High-Performance Liquid Chromatography (HPLC)**:

- HPLC can be used in combination with UV or fluorescence detectors to identify and quantify nitrosamines in drug products.

**Nuclear Magnetic Resonance (NMR) Spectroscopy**:

- NMR spectroscopy can provide structural information about nitrosamine impurities, helping to confirm their presence and identity.[16]

**Risk Management and Mitigation Strategies**

**Supplier Qualification and Audits**:

- Conduct regular audits and qualification processes for raw material suppliers to ensure that the materials provided are free from nitrosamine contamination.

**Process Analytical Technology (PAT)**:

- Implement PAT tools to monitor critical manufacturing parameters in real-time, allowing for immediate adjustments to prevent the formation of nitrosamines.

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**Employee Training and Awareness**:

- Train manufacturing personnel on the risks associated with nitrosamine impurities and the best practices for preventing contamination.

**Regulatory Compliance**:

- Stay updated with the latest regulatory guidelines and requirements related to nitrosamine impurities, ensuring that all manufacturing practices align with these standards.[17,18]

**Case Studies of Nitrosamine Contamination**

**Valsartan Recalls**:

- In 2018, several batches of valsartan, an angiotensin II receptor blocker (ARB), were recalled due to the presence of NDMA and NDEA impurities. The contamination was traced back to changes in the manufacturing process that introduced these nitrosamines.

**Ranitidine Contamination**:

- In 2019, ranitidine (Zantac) was found to contain NDMA impurities. The FDA issued warnings, and manufacturers voluntarily recalled the product. The contamination was linked to the instability of ranitidine, which could break down to form NDMA under certain conditions.

**Metformin Contamination**:

- Low levels of NDMA were detected in some metformin products used to treat diabetes. The FDA and EMA investigated and worked with manufacturers to ensure that affected products were identified and recalled.[19,20]

## III. FUTURE DIRECTIONS AND RESEARCH

**Developing New Analytical Techniques**:

- Research is ongoing to develop more sensitive and specific analytical techniques for detecting and quantifying nitrosamine impurities in pharmaceuticals.

**Green Chemistry Approaches**:

- Adopting green chemistry principles in drug manufacturing can reduce the use of nitrosating agents and minimize the risk of nitrosamine formation.

**Advanced Process Controls**:

- Implementing advanced process control systems and artificial intelligence (AI) can help predict and prevent the formation of nitrosamine impurities in real-time.

**Collaborative Efforts**:

- Encouraging collaboration between regulatory agencies, pharmaceutical companies, and research institutions can lead to the development of standardized guidelines and best practices for managing nitrosamine impurities.

By addressing these additional points, the pharmaceutical industry can further enhance its strategies for detecting, managing, and mitigating the risks associated with nitrosamine impurities, ensuring the continued safety and efficacy of drug products.[21-23]

## IV. CONCLUSION

The issue of nitrosamine impurities in drugs and medicines has emerged as a significant concern in the pharmaceutical industry. These impurities, which are potential carcinogens, can arise from various sources during the drug manufacturing process. Understanding these sources, such as raw materials, solvents, catalysts, and water supply, is crucial for implementing effective risk management strategies. Analytical methods, including Gas Chromatography-Mass Spectrometry (GC-MS), Liquid Chromatography-Mass Spectrometry (LC-MS), and High-Performance Liquid Chromatography (HPLC), play a vital role in detecting and quantifying nitrosamine impurities. The development and application of these techniques are essential for ensuring the safety of pharmaceutical products. Risk management and mitigation strategies are critical to preventing nitrosamine contamination. These strategies include thorough supplier qualification, process analytical technology (PAT), employee training, and strict regulatory compliance. Implementing

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these measures can significantly reduce the risk of nitrosamine impurities in drug products. Case studies of nitrosamine contamination, such as those involving valsartan, ranitidine, and metformin, highlight the importance of vigilance and swift action in addressing these issues. These examples demonstrate the need for continuous monitoring, investigation, and collaboration among regulatory agencies, pharmaceutical companies, and research institutions. Looking forward, the industry must focus on developing new analytical techniques, adopting green chemistry approaches, and implementing advanced process controls to further minimize the risk of nitrosamine impurities. Collaborative efforts will be essential in establishing standardized guidelines and best practices for managing these impurities. In conclusion, addressing the challenge of nitrosamine impurities requires a comprehensive approach that encompasses detection, prevention, and mitigation strategies. By leveraging advanced analytical methods, stringent risk management practices, and collaborative efforts, the pharmaceutical industry can ensure the continued safety and efficacy of its products, ultimately safeguarding public health.

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