ejpmr, 2025, 12(2), 413-419

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

NITROSOAMINE IMPURITY AS CARCINOGENIC

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Article Received on 21/12/2024 **Article Revised on 11/01/2025** **Article Accepted on 01/02/2025**

ABSTRACT

Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains nitrosamines at, or below, the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer. Ten nitrosamines found in food are carcinogenic (can cause cancer) and genotoxic (may damage DNA. DNA (deoxyribonucleic acid) is capable of copying itself and carries the instructions for all the proteins used to create and sustain life). Nitrosamines are a group of organic chemicals formed by the interaction of nitrites with amines or amides inside the body; they have been found to cause cancer in animals. The mechanism of carcinogenicity results from enzymatic α-hydroxylation with cytochrome P450 where dealkylated primary nitrosamine is formed. The unstable primary nitrosamine further decomposes to diazonium 3, a DNA alkylating agent, which is a carcinogen. N-nitrosamines are carcinogenic impurities most commonly found in groundwater, treated water, foods, beverages and consumer products. The recent discovery of N-nitrosamines in pharmaceutical products and subsequent recalls pose a significant health risk to patients. Initial investigation by the regulatory agency identified Active Pharmaceutical Ingredients (API) as a source of contamination. However, N-nitrosamine formation during API synthesis is a consequence of numerous factors like chemistry selection for synthesis, contaminated solvents and water. Furthermore, apart from API, N-nitrosamines have also been found to embed in the final product due to degradation during formulation processing or storage through contaminated excipients and printing inks. The landscape of N-nitrosamine contamination of pharmaceutical products is very complex and needs a comprehensive compilation of sources responsible for N-nitrosamine contamination of pharmaceutical products. Therefore, this review aims to extensively compile all the reported and plausible sources of nitrosamine impurities in pharmaceutical products. The topics like risk assessment and quantitative strategies to estimate nitrosamines in pharmaceutical products are out of the scope of this review.

KEYWORDS: DNA, carcinogen, genotoxic, nitrites, N-nitrosoamine, primary, secondary, tertiary amine, quaternary amine.

INTRODUCTION

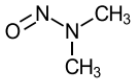
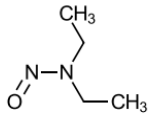
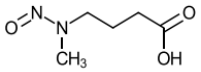
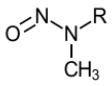
This guidance recommends steps manufacturers and applicants of active pharmaceutical ingredients (APIs) and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in drug products. The guidance also describes conditions that may introduce nitrosamine impurities. The unexpected finding of nitrosamine impurities, which are probable or possible human carcinogens, in certain drug products has made clear the need for a risk assessment strategy for the potential presence of nitrosamines in any drug product.[1-10]

Root cause of nitrosamine impurity

(A) The term nitrosamine describes a class of compounds having the chemical structure of a nitroso group bonded to an amine (R1 N(-R2)-N=O), as shown in Figure 1. The compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions). A different class of precursor is 1,1-disubstituted hydrazine, which can be oxidized to form a nitrosamine. The compounds 1-cyclopentyl-4-nitrosopiperazine and 1-methyl-4-nitrosopiperazine are formed via this hydrazine oxidation process.

Chemical classification

Table 1: N-nitrosamines.

Nitrosamine	Structure	Cancer Classification [1]
N-Nitrosodimethylamine (NDMA, NMA-C1)		IARC 2A (1987) US EPA B2 (1986) NTP RoC RA (1981) P65 (1987)
N-Nitrosodiethylamine (NDEA)		IARC 2A (1987) US EPA B2 (1986) NTP RoC RA (1981) P65 (1987)
N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)		Not evaluated
N-Nitrosomethylethylamine (NMA-C2) N-Nitrosomethyl-*n*-propylamine (NMA-C3) N-Nitrosomethyl-*n*-butylamine (NMA-C4) N-Nitrosomethyl-*n*-pentylamine (NMA-C5) N-Nitrosomethyl-*n*-hexylamine (NMA-C6) N-Nitrosomethyl-*n*-heptylamine (NMA-C7) N-Nitrosomethyl-*n*-octylamine (NMA-C8) N-Nitrosomethyl-*n*-nonylamine (NMA-C9) N-Nitrosomethyl-*n*-decylamine (NMA-C10) N-Nitrosomethyl-*n*-undecylamine (NMA-C11) N-Nitrosomethyl-*n*-dodecylamine (NMA-C12) N-Nitrosomethyl-*n*-tetradecylamine (NMA-C14)	 R: alkyl group (where C2 indicates a 2 carbon alkyl group, C3 indicates a 3 carbon alkyl group, and so on)	NMA-C2: IARC 2B (1987) US EPA B2 (1988) P65 (1989) NMA-C3 through NMA-C12, and NMA-C14: P65 (2014)

Root Causes of the Presence of Small-Molecule Nitrosamine Impurities in APIs

(B) Information gathered by FDA suggests several general root causes of the presence of nitrosamine impurities in APIs.

General Conditions That Lead to Nitrosamine Formation: Formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines 20 and nitrite salts 21 under acidic reaction conditions. Under these conditions, nitrite salts may form nitrous acid, which can react with an amine to form a nitrosamine. There is a greater risk of nitrosamine formation if nitrous acid is used to quench residual azide (a reagent commonly used in tetrazole ring formation or introduction of azide functional group into a molecule) in the presence of precursor amines.

Nitrites used as reagents in one step can carry over into subsequent steps, despite purification operations, and react with amines to generate nitrosamine impurities. Therefore, whenever nitrite salts are present, carryover into subsequent steps cannot be ruled out. In general, processes that use nitrites in the presence of secondary, tertiary, or quaternary amines are at risk of generating nitrosamine impurities.

(C) Sources of Secondary, Tertiary, and Quaternary Amines That Can Form Nitrosamines: Amines may be present in a manufacturing process for a variety of reasons. The API (or API degradants), intermediates, or API raw materials 22 may contain secondary or tertiary amine functional groups. Tertiary and quaternary amines may also be added intentionally as reagents or catalysts. All of these types of amines can react with nitrous acid or other nitrosating agents to form nitrosamines. Amide solvents, which are susceptible to degradation under certain reaction conditions, are another source of secondary amines. For example, under high reaction temperatures for an extended reaction period, N,N-dimethylformamide can degrade into dimethylamine, which can react with nitrous acid to form NDMA. N-methylpyrrolidone, N,N-dimethylacetamide, and N,N-diethylacetamide also have similar degradation pathways to form secondary amines that can react with nitrous acid to form nitrosamine impurities. Secondary amines could also be present as impurities in amide solvents. For example, dimethylamine, which can react with nitrous acid to form NDMA, may exist as an impurity in N,N-dimethylformamide.

(D) Vendor-Sourced Raw Materials Containing Nitrosamine Impurities: Nitrosamine impurities can be introduced when vendor-sourced raw materials contain nitrosamines or precursors. The Agency has observed the following root causes of nitrosamine impurities in vendor-sourced materials

- Nitrosamines have been found in fresh solvents (ortho-xylene, toluene, and methylene chloride) when impurities were carried over during transfer between storage vessels used in the shipment of solvents.

- Sodium nitrite is a known impurity in some starting materials (such as sodium azide) and may be present and react with amines under acidic conditions to form nitrosamines. Nitrate-containing raw materials, such as potassium nitrate, may contain nitrite impurities. The amount of nitrite impurity that can be tolerated is process-dependent and should be determined by each API manufacturer.

- Secondary or tertiary amines have been reported as impurities in some raw materials (see details in section III.B.2.) and in fresh solvents such as toluene.

Awareness of the supply chain of API raw materials is an important factor in preventing nitrosamine impurities and cross-contamination of APIs. For example, without supplier oversight, API manufacturers may not be aware of nitrosamine impurities or precursors in API starting materials they have sourced from vendors; a manufacturer whose process is not normally susceptible to nitrosamine formation may not realize that vendor-sourced material may have had impurities introduced during production or transport.

(E) Recovered Solvents, Reagents, and Catalysts as Sources of Nitrosamine Impurities: Recovered materials such as solvents, reagents, and catalysts may pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine). If the recovery process involves a quenching step (i.e., nitrous acid used to decompose residual azide), nitrosamines could form during solvent recovery. These nitrosamines may be entrained if they have boiling points or solubility properties similar to the recovered materials, depending on how recovery and subsequent purification takes place (e.g., aqueous washes or distillation). This further increases the risk of nitrosamines in material recovery. For these reasons, some drug products using APIs manufactured by certain "low" risk processes were found to contain nitrosamine impurities. The Agency has observed the following due to this root cause:

- A manufacturing site may produce the same API by more than one synthetic process that uses common solvents. If any of those synthetic processes produces nitrosamines or contains precursor amines, the solvents sent for recovery are at risk. The use of recovered solvents that are commingled from different processes or across manufacturing lines without control and monitoring can introduce nitrosamine impurities. If a recovered solvent with nitrosamine impurities is used to manufacture an API, the API will contain the impurities even if the synthetic route is not normally susceptible to nitrosamine formation.

- Recovery of raw materials (e.g., solvents, reagents, and catalysts) is often outsourced to third-party contractors. Process outsourcing can pose a risk if the third-party recovery facility does not receive enough specific information on the contents of the materials it is processing and relies solely on routine recovery processes.

- Raw materials can contain nitrosamine impurities if adequate cleaning of equipment between customers, or between different materials, is not carried out or is not validated as capable of removing each impurity of concern. It was reported that nitrosamine impurities were introduced into recycled ortho-xylene and toluene due to inadequate cleaning and use of shared storage equipment between different customers. Inadequate and unvalidated cleaning procedures can also lead to cross-contamination if precautions to avoid nitrosamines are not in place before materials from different customers are combined for recovery. For example, nitrosamine impurities were introduced into lots of the catalyst triN-butyltin chloride (used as a source of tri-N-butyltin azide) at a third-party contractor facility due to the combining of catalyst lots from multiple customers.

(F) Quenching Process as a Source of Nitrosamine Impurities: There is a risk of nitrosamine formation when a quenching step is conducted directly in the main reaction mixture (i.e., when nitrous acid is added to the reaction mixture to decompose residual azide). This allows nitrous acid to come into direct contact with residual amines in the raw materials used in the manufacturing process. The nitrosamine impurities could be carried to the subsequent steps if adequate removal or purification operations are not in place, or if the operations are not optimized for removing specific impurities of concern. These impurities can enter the downstream process once they are introduced. Even if the quenching process is conducted outside of the main reaction mixture there is a risk if recovered materials containing nitrosamine impurities are introduced into the main process.

(G) Nitrosamine Impurities in Drug Products From Sources Other Than APIs: Nitrites are common nitrosating impurities that have been reported in many excipients at parts per million (ppm) levels. Nitrite impurities are found in a range of commonly used excipients, which may lead to nitrosamine impurities forming in drug products during the drug product manufacturing process and shelf-life storage period. A manufacturer's supplier qualification program25 should take into account that nitrite impurities vary across excipient lots and may vary by supplier. Drug product manufacturers and applicants should also be aware that nitrite and nitrosamine impurities may be present in potable water. Additionally, when nitrosamine precursors such as secondary, tertiary, and quaternary amines, including API fragments, exist as impurities in a drug substance, these precursors can react with nitrites in excipients or nitrites from other sources used in the manufacturing process and form small-molecule nitrosamines or NDSRIs in drug products. Some container closure systems, including secondary packaging components, and manufacturing equipment could be a source of nitrite or nitrosamine impurities. These impurities may leach into the drug products during manufacturing or storage resulting in small molecule nitrosamine impurities or NDSRIs. The risk for such impurities should be assessed during extractable and leachable studies.[11-20]

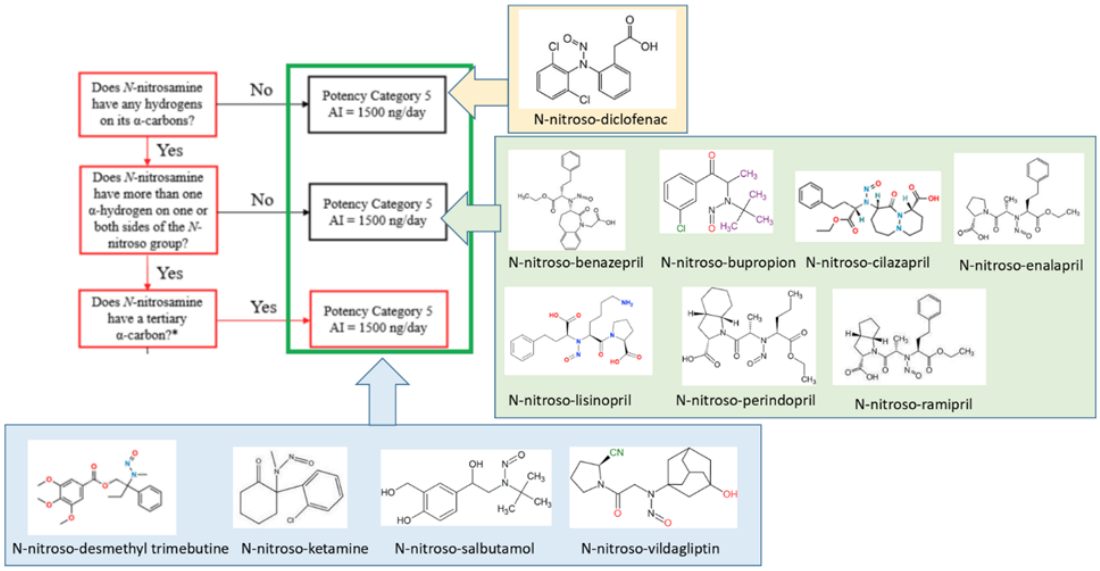


Figure 1: Nitrosamine biochemical pathway.

Structure Activity Relationship [SAR]

- H- on alpha position carbon atom increase the potency of carcinogen.
- The CH_3 on beta carbon increase the potency.
- The aryl group in alpha carbon increase the potency.
- - OH group in beta carbon decrease potency.
- - COOH group in molecule decrease potency.
- The pyrrolidine ring decrease the potency of carcinogen.
- The EWG group decrease the potency.
- The chain structure in molecule decrease the potency.

The N=O is Responsible for DNA damage, that leads to cancer in Human body.

Table 2: Nitrosamine adverse effect.

Drug Class and Major Indication	Active Pharmaceutical Ingredient (Dose per tablet)	NDMA (μg/tablet)	NDEA (μg/tablet)
Angiotensin II receptor blockers (ARBs): hypertension and related heart conditions	Valsartan (160 mg) *	0.45	1.31
	Valsartan (320 mg) *	<LOD–20.19	<LOD–1.22
Histamine-2 blockers: heartburn and gastroesophageal reflux disease (GERD)	Ranitidine (75 mg) **	0.01–0.04	NR
	Ranitidine (150 mg) **	0.01–0.33	NR
	Ranitidine (300 mg) **	0.01–0.86	NR
	Nizatidine (150 mg)	0.01–0.02	NR
	Nizatidine (300 mg)	0.01–0.03	NR
Antihyperglycemic: type 2 diabetes	Metformin, extended release (500 mg) *	<LOD–0.19	NR
	Metformin, extended release (750 mg) *	0.01–0.08	NR
	Metformin, extended release (1000 mg) *	<LOD–0.01	NR
	Metformin, immediate release (500 mg)	<LOD	NR
	Metformin, immediate release (850 mg)	<LOD–0.01	NR
	Metformin, immediate release (1000 mg)	<LOD	NR

LOD: limit of detection; NR: not reported; * recalled; ** withdrawn from the market. [1] Information presented in the table is from US FDA as of July 2021 (See References [58–60]).

Public Health Concerns: Carcinogenic nitrosamine contaminants have been detected in medications that include first-line treatments for prevalent chronic conditions such as hypertension (ARBs), heartburn (histamine-2 blockers), and type 2 diabetes (metformin). This is a public health concern, given that tens of millions of Americans with these conditions may have been treated with affected medications. For example, hypertension is estimated to affect 116 million American adults, with the highest prevalence in the Black population, and over 83.4 million prescriptions for ARBs were issued in 2018. The second group of affected medications, histamine-2 blockers, had over 25.2 million prescriptions issued in the US in 2018, in addition to its availability in a number of OTC preparations. Histamine-2 blockers are a first-line treatment option for medical management of heartburn, which is estimated to affect at least 60 million Americans once a month and 15 million Americans on a daily basis.[21-30] The use of the antihyperglycemic drug metformin is similarly widespread, with nearly 83.8 million prescriptions written for metformin hydrochloride alone in the US in 2018 . Metformin is a first-line treatment for type 2 diabetes, which is estimated to affect as many as 34.2

million Americans, with higher prevalence in nonwhite populations. Metformin is also increasingly prescribed for treatment of endocrine, cardiovascular, and other metabolic disorders. Given the extensive use of these medications in the US, there is widespread potential for exposure to unacceptable levels of carcinogenic nitrosamine contaminants if the contamination is not controlled. Additional consideration is warranted for individuals taking more than one such medication simultaneously for management of multiple conditions, which may result in increased exposure to these carcinogenic contaminants across different medications. Additionally, individuals may be more or less susceptible to development of cancer as disease results from a combination of fixed and variable intrinsic factors (e.g., sex, epigenome, nutritional status) and potentially modifiable extrinsic factors (e.g., occupational exposures, racism and other psychosocial stressors, physical activity, diet) that comprise all biologically relevant external stressors. The fact that some of these affected medications are first-line treatments for conditions that disproportionately impact populations with health disparities who may be more susceptible, should be of public health concern. US FDA notes that nitrosamine impurities should not be present in drugs as they may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time. In 2019, the agency set interim acceptable daily intake limits for nitrosamines based on a cancer risk of 1 in 100,000, e.g., 0.096 µg/day for NDMA and 0.0265 µg/day for NDEA. These levels attempt to "balance the risks of potential long term carcinogenic risk and disruption to clinical management of patients' hypertension and heart failure" and other conditions. As evidenced by the large number of drug recalls, these interim levels have been exceeded numerous times, and discovery of additional nitrosamine-contaminated drugs has continued seemingly unabated. In this paper, we first provide a review of the evidence of carcinogenicity for these contaminants and other related nitrosamines. Next, to illustrate the potential public health impact, we use valsartan as a case study to estimate the additional cancer risk to individuals taking this medication, based on US data (i.e., US FDA-reported levels of NDMA and NDEA contamination) and likely exposure durations. A similar approach using European data has been taken by the European Medical Association.

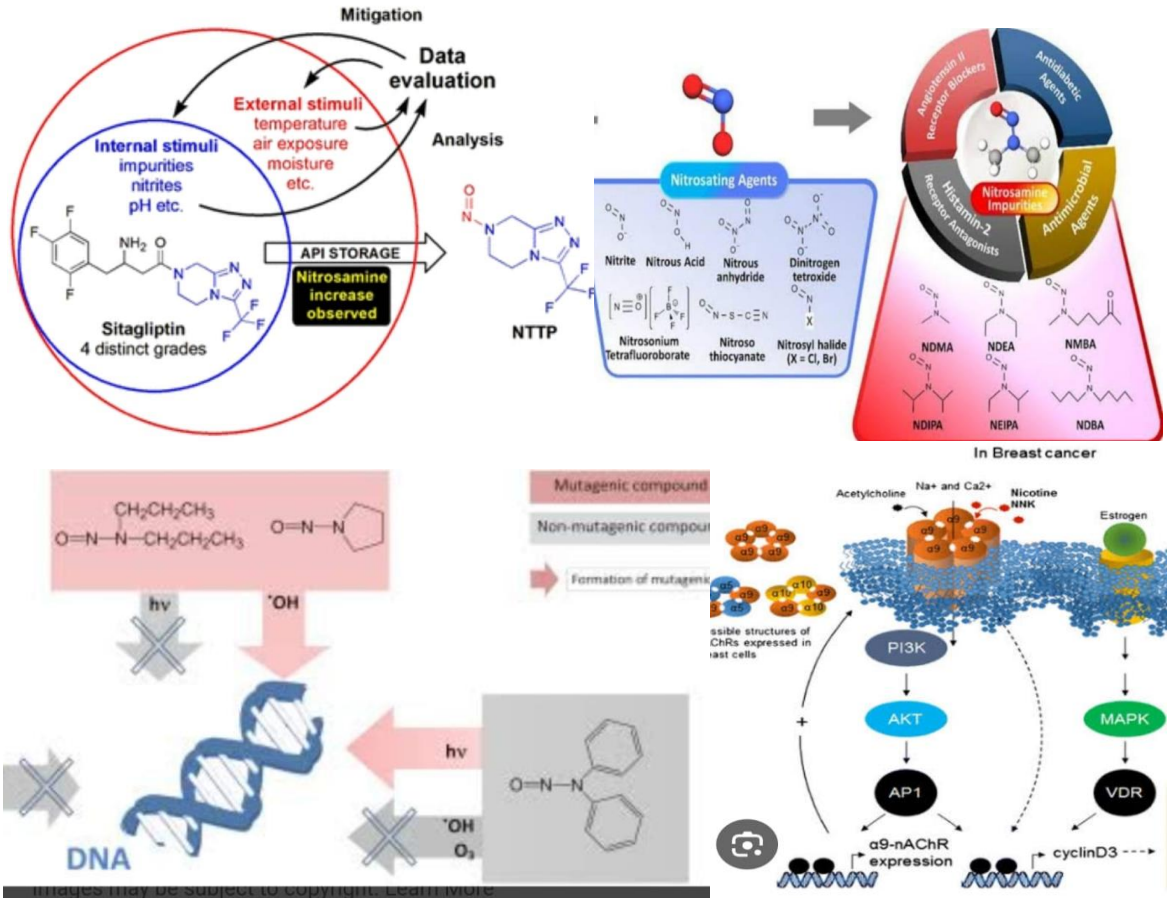


Figure 2: Nitrosamine combines with DNA.

Cancer Risk Estimate: To quantify the potential impact from taking these nitrosamine-contaminated medications, we calculated the cancer risk based on the nitrosamine levels reported by US FDA. While detections of NDMA and NDEA have been reported in a large number of drugs, contaminant levels have only been reported for a

few, with levels varying among drug products. In the case of NMBA, it has been detected in losartan and valsartan products, but concentrations of NMBA present in these products have not been reported. As shown in Table 4, the highest level of NDMA reported by US FDA was 20.19 µg per tablet in a valsartan product, and the highest level of NDEA was 1.31 µg per tablet, also in a valsartan product. These nitrosamine levels far exceed US FDA's interim acceptable intake limits of 0.096 µg/day for NDMA and 0.0265 µg/day for NDEA.[31-35]

Why it's important: Even small changes to pharmaceutical manufacturing processes risk introducing unsafe nitrosamine levels in medicines. Manufacturers can use USP solutions to detect and measure nitrosamines as well as verify the performance of their analytical procedures that monitor nitrosamine levels in their products. Detection, identification, and measurement enables manufacturers to control nitrosamine levels, as recommended by the regulators, protect patients, and reduce the likelihood of recalls and shortages. From a business perspective, it protects brand reputations and their bottom line. USP solutions help regulators better understand nitrosamine impurities and consistently measure their levels and manage public health risk.

CONCLUSION

Our risk analyses underscore the importance of preventing nitrosamine contamination from occurring in widely used drugs, and the necessity of removing contaminated drug products from the market. Prompt manufacturing changes and continued monitoring by US FDA are needed to address this serious public health issue. Ultimately, the presence of carcinogenic contaminants in drugs may affect treatment preferences, patient compliance, and health outcomes.

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