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# A REVIEW ON NITROSAMINE IMPURITY- SOURCES, ANALYTICAL METHODS, CARCINOGENICITY AND PRESENCE IN VARIOUS DRUGS

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**Abstract:**

*The presence of N-nitrosamines in pharmaceutical products has caused concern among health regulators and pharmaceutical companies. When nitrates or nitrites react with amines, nitrosamines are formed. Nitrosamines and/or their precursors are present in a variety of consumer items. Some sartan pharmaceutical products were discovered to be contaminated with nitrosamine compounds, which are very carcinogenic. Special emphasis was paid to N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA). The most prevalent Nitrosamines detected are NDMA and NDEA, however there are numerous more Nitrosamines as well. Certain nitrosamines may increase the risk of cancer if people are exposed to them at higher-than-safe levels for an extended period of time. People who consummate NDMA-containing drugs at or below the permissible consumption limits on a daily basis for 70 years are unlikely to get cancer. They can be present in medications, cosmetics, water, and food. Many variables contribute to the development of N-nitrosamine. The Food and Drug Administration classifies two Tobacco Specific Nitrosamines (TSNA) as dangerous and potentially harmful components (HPHCs) in tobacco products and tobacco, N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Many approaches for detecting nitrosamine have been developed since 1954.*

***Keywords:*** *Nitrosamine; NNK; NDMA; NDE; NNN; TSNA*

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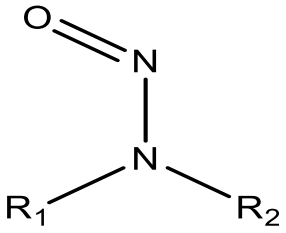
## INTRODUCTION:

On February 24, 2021, the FDA issued a guideline for the "Control of Nitrosamine Impurities in Human Drugs" (1). The FDA has published two techniques for assessing NDMA impurities: the LC-HRMS method and the LC-MS/MS (triple-quadrupole MS method). The FDA ordered that all ranitidine drugs, including Zantac, be removed from the market in the United States by April 1, 2020 (2). In September 2019, the (FDA) issued a voluntary recall request to manufacturers for ranitidine and nizatidine products having NDMA levels above what the Agency considers acceptable. Several medications, including Angiotensin Receptor Blockers (ARBs), ranitidine, nizatidine, and metformin, have been shown to have harmful amounts of nitrosamines as of 2018. According to FDA research, NDMA levels rise with increased storage time (3).

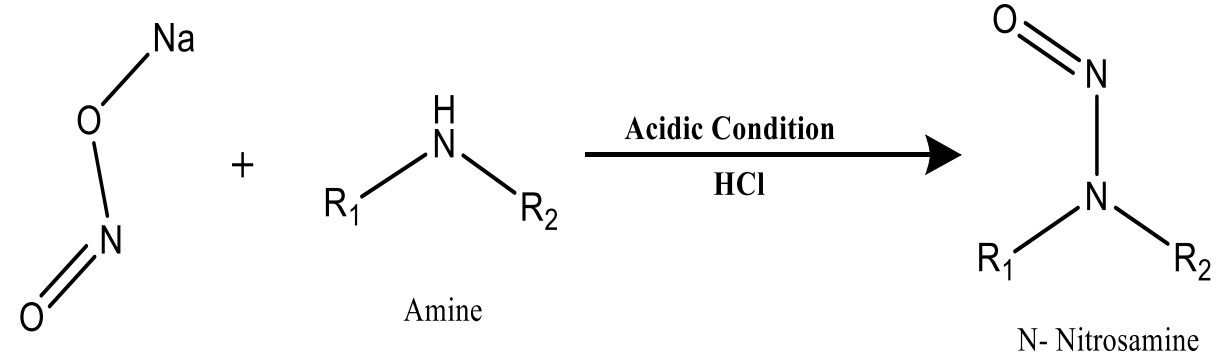
The stability of the active pharmaceutical ingredient (API) and the impurity levels in any medicinal product are critical variables. N-nitrosoamines (nitrosamines) in pharmaceutical goods have come under investigation as a consequence of the July 2018 finding of N-nitroso dimethylamine (NDMA) in valsartan. NDMA and other similar nitrosamines were discovered in more sartan medications during the next several months, as well as in other product categories and prescriptions such as ranitidine. Health officials issued recommendations mandating marketing authorization holders (MAHs) to complete nitrosamine risk assessments for all synthetic medicinal items on the market, as well as confirmatory testing and changes to the production process or control strategy if necessary. (4). The ICH M7 guideline describes how to manage the risks associated with the presence of potentially mutagenic impurities (PMIs) in pharmaceutical substances. The hazards of PMIs are typically associated with the use of highly reactive reactants and reagents, which are essential to permit successful syntheses of the desired active pharmaceutical ingredient (API) and are investigated throughout pharmaceutical research. Highly reactive reactants and reagents are both desired and required during production; if PMIs are not effectively removed from the completed medicinal product, they may cause DNA mutation in vivo, leading to mutagenicity (5). The pharmaceutical research and manufacturing association (PhRMA) has compiled a list of functional groups known to interact with DNA. (6).

This review is made for understanding the source of nitrosamines, analytical methods for detecting Nitrosamine, their carcinogenicity. In this review authors made an attempt to know the various reactions and classification of Nitroamines along with their impact on human beings if it is exceeded their limit in the product.




General Structure of Nitrosamine

**General Reaction**



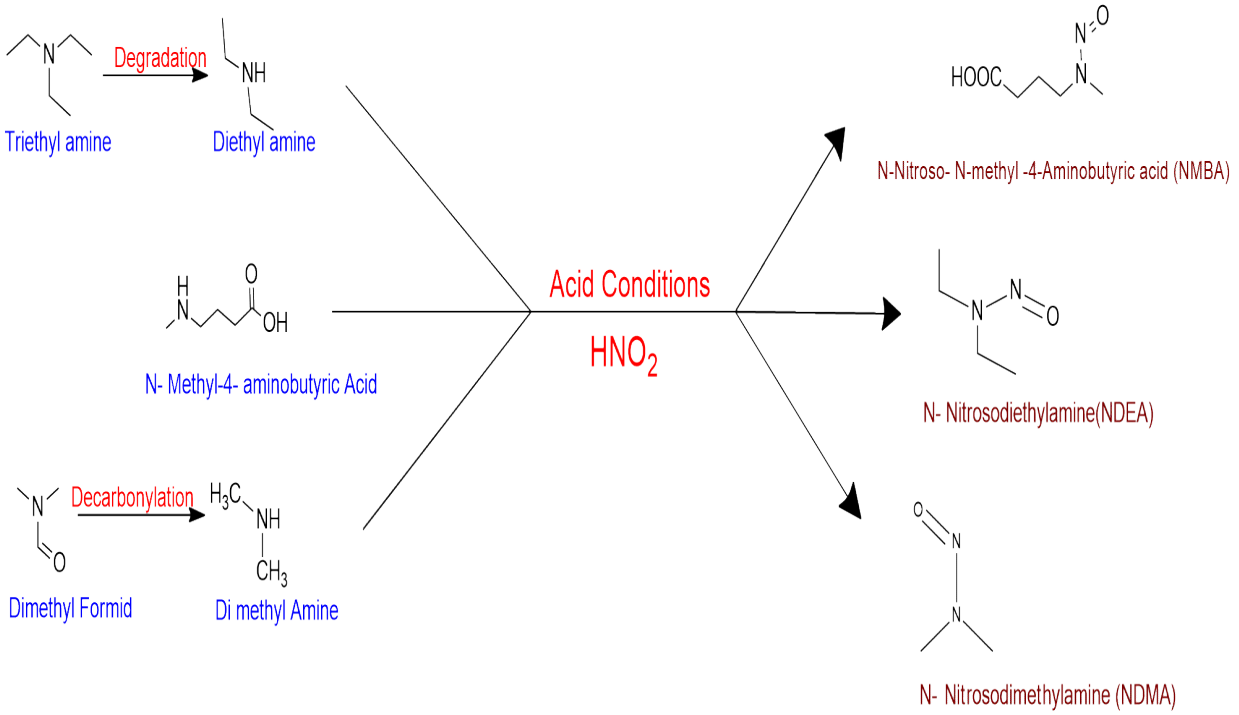

Sodium Nitrite Amine N- Nitrosamine

**Sources of contamination**

Contaminants such as nitrosamine are possible sources in medications. Based on the flow of the pharmaceutical manufacturing process, the numerous root causes of nitrosamine contamination may be loosely divided into three groups, namely processes linked to API synthesis, product manufacture, and packaging. The body may manufacture nitroso compounds in the organs of persons who did not come into touch with nitrites or nitrates, as well as primary, secondary, and tertiary amines, according to information (7,8).

**Major causes for nitrosamine Impurities**

The presence of nitrosamines in medications beyond certain thresholds is prohibited since they frequently cause cancer in the environment. The FDA has issued a guidance sheet outlining the toxic nitrosamines and their acceptable levels. The pharmacovigilance investigation discovered inadequate amounts of nitrosamine contaminants in some of the goods, resulting in market recalls. The primary precursors for the formation of nitrosamines are sodium nitrite and secondary amine(s) (9).




**Formation of N-nitrosamine from amines**

**Amines**

Nitrosamine does not develop from primary amine. An aliphatic primary amine is nitrosated to yield an alkyl diazonium ion and water. A nitrosation process takes place with secondary amines. The secondary amine's basicity influences its reactivity. Amines of all types undergo the nitrosation process. Nitrosamines can also be formed by hydrolysis of tertiary amines and secondary amines. Twelve regularly used tertiary amine medications react with nitrite to produce dialkyl nitrosamine, which is a known carcinogen when the pH of an aqueous solution is between 3 and 4. Three distinct nitroso compounds made from asymmetric tertiary amines by nitrative cleavage or nitrative dealkylation (10).

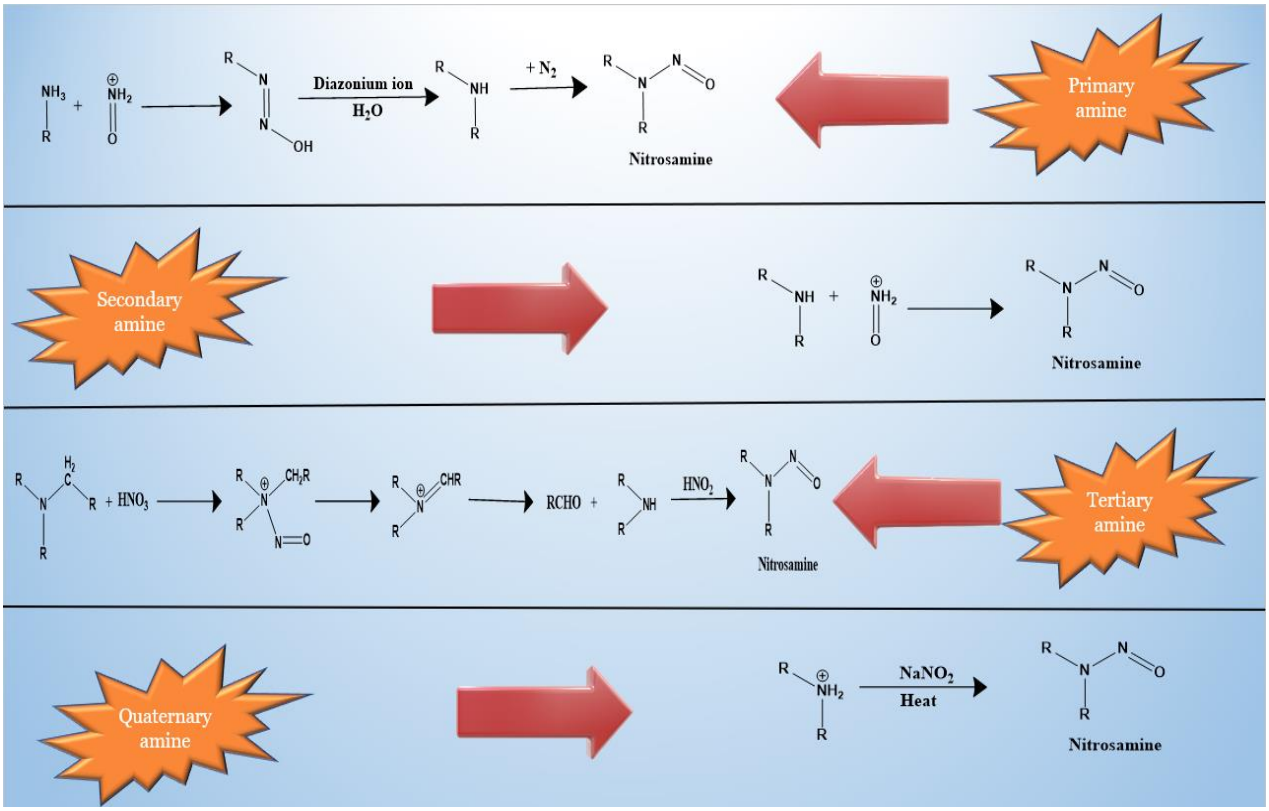



*Figure 1 Pathways for Formation of N- Nitrosamine from amines (11)*

**Water**

The first studies establishing the presence of NDMA in aquatic settings were published in the 1970s. The final disinfection of drinking water has emerged as the primary source of nitrosamines in the twenty-first century. It was once believed that NDMA production was caused by chloramination. The water of chlorinated swimming pools has also been discovered to contain nitrosamines. Since only chemicals containing organic nitrogen can form nitrosamines during water treatment (and distribution), nitrosamine precursors are the main problem in the production of NDMA. Secondary amines are most important for the formation of nitrosamine impurities in water. It has been established that the reactions involve the species of $N_2O_3$, $H_2ONO+NO+$, and XNO. When the pH is acidic, the reaction moves along most quickly at pH 3.4 (12).

**Nitrate salts**

According to preliminary research on the interaction of tertiary amines with nitrous acid, tertiary amines typically undergo the nitrosative dealkylation process at a slightly acidic pH to create dialkyl nitrosamines. Because nitrite is commonly used to preserve and cure meat and fish and can be created by the reduction of nitrate, such reactions occurring in the human stomach may be a source of carcinogenic nitrosamines (13).

These impurities may occur in trace amounts because of the degradation of the solvent or other materials employed in the medicinal compounds' manufacture. Similarly, contaminants called nitrosamines may be added to drug compounds as by-products of the medication production process.

**Packaging**

Specific packaging materials used for finished items may include nitrosamine impurities. One theory state that nitrocellulose-containing packaging lidding foil may react with the amines in the printing ink to produce Nitrosamine impurities, which may then be transferred to the drug product (14). They are Different types of nitrosamines which can be classified based on their carcinogenic Potential.

**Based on the Carcinogenic Potential**

| Carcinogenic Potential | |
|---|---|
| **Group 1** | Substances that have been shown to cause human cancer |
| **Group 2** | Significant evidence in experimental animals but limited data in people that are likely human carcinogens. With scant evidence in both humans and laboratory animals |
| **Group 3** | Drugs may cause human cancer |
| **Group 4** | Insufficient data on their carcinogenicity in humans and experimental animals, agents that cannot be classified as to their carcinogenicity to humans (15). |

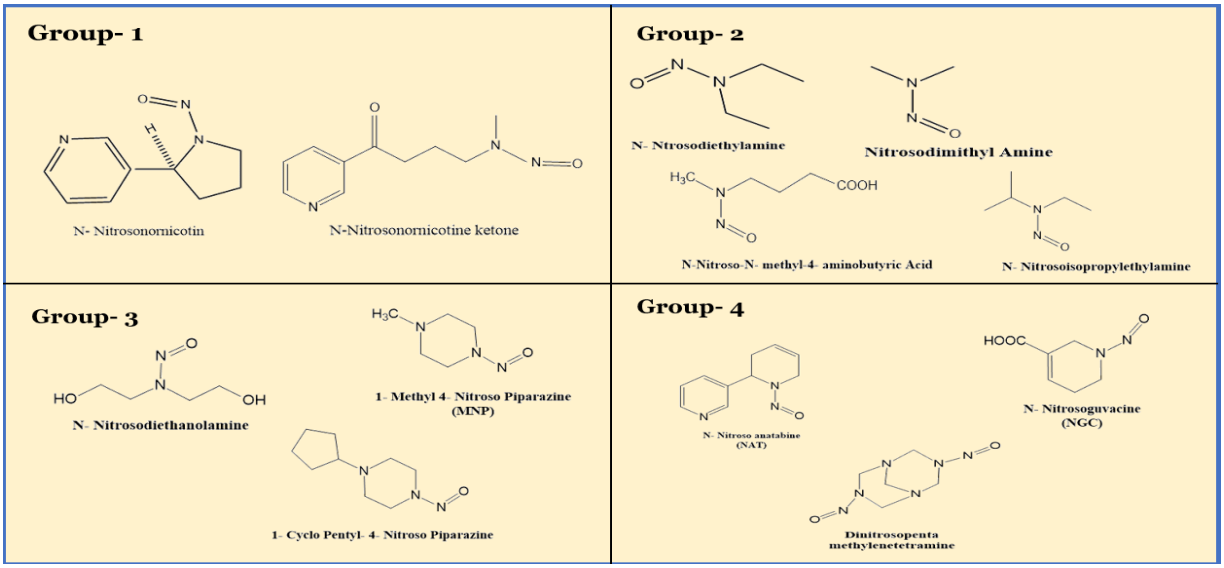



**Figure 2 Classification According to IARC (International Agency for Research on Cancer (IARC)) Monographs**

**Nitrosamine Carcinogenicity**

Barnes and Magee discovered N-nitrosodimethylamine (NDMA), the simplest dialkylnitrosamine, in 1954 (16). Some nitrosamines are exceptionally potent carcinogens, capable of developing tumors at extremely low dosages. Dose-response tests on NDMA and N-nitrosodiethylamine (NDEA) delivered in drinking water, for example, were conducted using 4080 rats. Another significant fact is that nitrosamines typically cause tumors at specific places regardless of the delivery method. At dosages less than 1 ppm, a linear association was seen. Thus, a dose of 1 ppm resulted in around 25% of the rats developing a liver tumor, 0.1 ppm in approximately 2.5%, and so on, with no indication of a threshold (17).

**Carcinogenic N- Nitrosamine In food**

The total N-nitrosamines found in food were assessed to be 6.7 0.8 ng/g on average, ranging from 0 to 120.8 ng/g (18).

| Nitrosamine | ng/g |
|---|---|
| **NDMA** (N-nitrosodimethylamine) | 2.2±0.3 ng/g |
| **NDBA (**N- nitroso di n- butylamine) | 1.5±0.5 ng/g |
| **NPYR** (N- nitroso pyrrolidine) | 1.5±0.2 ng/g |
| **NDEA** (N- nitroso diethyl amine) | 0.9±0.3 ng/g |
| **NPIP** (N- nitroso piperidine) | 0.5±0.1 ng/g |
| **NMOR** (N- nitroso morpholine) | 0.05± 0.01 ng/g |
| **NMEA** (N- nitroso methylethyl amine) | 0.04±0.01 ng/g |
| **NDPA** (N- nitroso di n- propylamine) | 0.02±0.01 ng/g |

**Carcinogenic Nitrosamine in Drugs**

The United States Food and Drug Administration (FDA) has discovered five N-nitrosamines found in drugs: NDMA, NDEA, N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitroso-isopropylethylamine (NIPEA), and N-nitrodiisopropylamine (NDIPA). Two more N-nitrosamines, NDBA and N-nitrosomethylphenylamine (NMPA), are thought to be found in medicinal products. Acceptable intake limits for the carcinogenic N-nitrosamines are 96 ng/day (NDMA) and 26.5 ng/day (NDEA), according to the FDA (19).

**Carcinogenic Nitrosamine in Cosmetic**

The number of N-nitrosamines found in cosmetics was estimated to be 1507 752 ng/g, with concentrations ranging from 0 to 49,000 ng/g. NDELA (N-Nitroso diethanolamine) is responsible for 99% of the total N-hellonitrosamines in these items. It was primarily responsible for the relatively high amounts of N-nitrosamines found in cosmetics such as hair care products, soaps, shampoos, lotions, and others. (18) NDELA is produced by nitrosation of triethanolamine and diethanolamine, commonly used in cosmetics and nitrosating chemicals such as nitrite. (20,21)

**Carcinogenic Nitrosamine in Water**

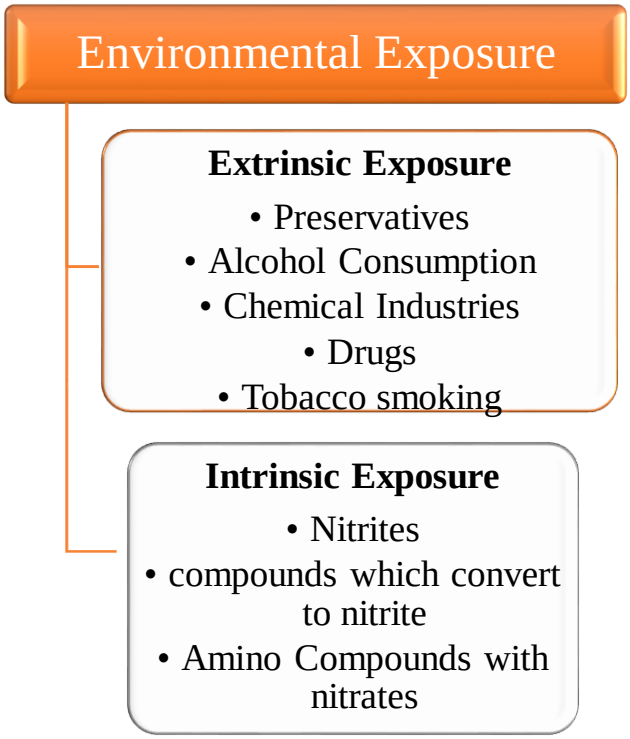
NDMA has been found in drinkable water, raising regulatory worries about its presence in drinking water. The presence of NDMA is thought to be caused by chloramination in the disinfection of water. (22,23) Average of 39.4 ± 10.5 ng/L; range: 2.8–309.0 ng/L

| Nitrosamine | ng/g |
|---|---|
| **NDMA** (N-nitrosodimethylamine) | Average 17.7±4.7 ng/L |
| **NDBA** (N- nitroso di n- butylamine) | 1.7 ± 0.6 ng/L |
| **NPYR** (N- nitroso pyrrolidine) | 5.5 ± 2.6 ng/L |
| **NDEA** (N- nitroso diethyl amine) | 4.2 ± 0.8 ng/L |
| **NPIP** (N- nitroso piperidine) | 7.9 ± 4.0 ng/L |
| **NMOR** (N- nitroso morpholine) | 0.9 ± 0.2 ng/L |
| **NMEA** (N- nitroso methylethyl amine) | 0.6 ± 0.1 ng/L |

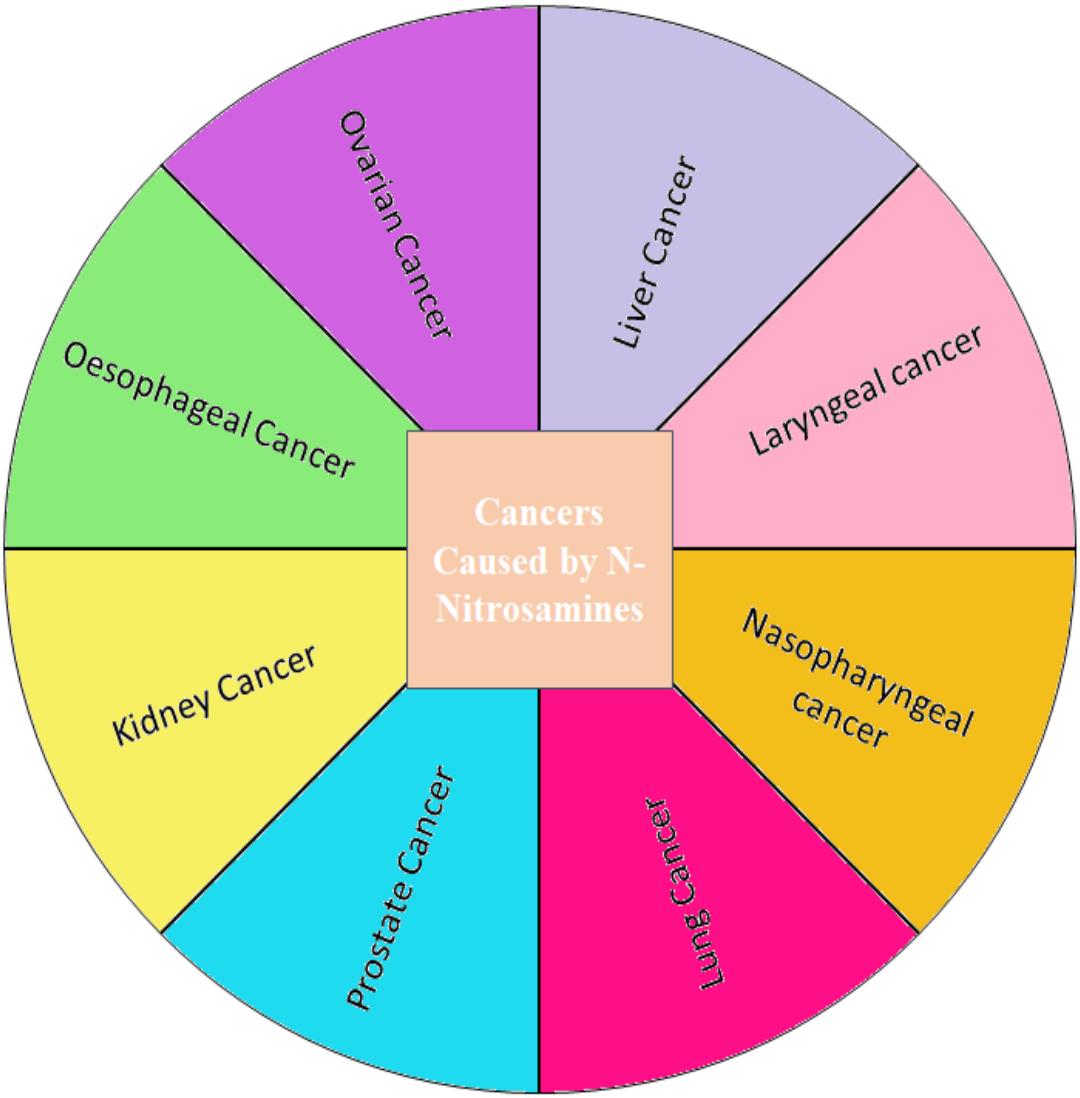
**Nitrosamine in food products**

Research done by **Distribution of Seven N-Nitrosamines in Food** (Jong-eun Park et al) reported that NDMA and NDEA were the most found in agricultural food products. NDMA (N-nitrosodimethylamine), NDBA (N- nitroso di n-butylamine), and NMOR (N- nitroso morpholine) were found in fisheries products, but at extremely low levels. Milk and milk products had no detectable levels of any of the tested nitrosamines. Cheese had an NDMA (N-nitrosodimethylamine) content of 0.72 g/kg, while cake and ice cream had less than 0.56 g/kg. The highest detection rate of NDMA was found in meat and meat products. Nitrosamine concentrations were highest in seasoning samples, with 13.48 g/kg of NDMA and 6.53 g/kg of NPIP (N- nitroso piperidine). Because prior study on nitrosamines in seasoning is limited, the mechanism of formation in relation to the manufacturing process needs to be researched further. NDMA levels in sauce samples were determined to be 3.02 g/kg. On average, 1 g/kg of NDMA was identified in oil samples. NDMA was found in all samples, and NMOR was found in soybean, olive, canola, rape, and sun follower oil; however, additional nitrosamines were not found. On average, 1 g/kg of NDMA was identified in oil samples. NDMA was found in all samples, and NMOR was found in soybean, olive, canola, rape, and sun follower oil; however, additional nitrosamines were not found in the research. (24)

It was discovered around 40 years ago that foods cooked with sodium nitrite included N-nitroso compounds, which cause the formation of nitrosodimethylamine, which is toxic to the livers of animals. To measure varied N-nitrosamine levels, 38 liquors and 215 food supplements cooked according to standard human consumption standards were used. The appropriate levels were discovered for 80 (31.5%) of the samples. According to research studies, men consumed 0.015 g of N-nitrosopiperidine (NPIP), 0.011 g of N-nitroso pyrrolidine (NPYR), and 0.28 g of N- nitrosodimethylamine (NDMA) each day, whereas women consumed 0.015 g of NPIP, 0.011 g of NPYR, and 0.17 g of NDMA per day. Consumption of beer contributed to 31% of males' daily NDMA exposure. (25)



**Environmental Exposure Types of Cancers Caused by N- Nitrosamines**



**Presence of Nitrosamine in Various Drugs:**

| Class of Drug | Nitrosamine Formation | Drugs in which There is High risk of nitrosamine formation |
|---|---|---|
| **ARBs** | Nitrosamine in ARBs is commonly formed during the manufacturing of APIs and is classified as an in-process impurity since it contains the Triazole ring. | valsartan, losartan, irbesartan, candesartan, and olmesartan |
| **Histamine- 2 Receptor Antagonists** | The contamination during the manufacturing process, the inherent instability of APIs, and drug contaminant degradation are all factors to consider. When a nitro Functional Group and the presence of a DMA side chain combine to generate NDMA. | Ranitidine and Nizatidine |
| **Antidiabetic Drugs** | NDMA is produced during the production process of metformin medicinal products, according to Nasr et al. (2021). Nitrites and nitrates found in pharmaceutical excipients such as CMC sodium, HPMC E5, HPMC K15M, and PolyoxTM are important nitrosamine contaminating contributors. Excessive humidity in wet granulation and extreme temperatures during the drying phase cause nitrosation reactions in the metformin tablet manufacturing process. | Metformin |
| **Anti-Microbial Drugs** | The contaminated nitrosamines are structurally related to the APIs, implying that two nitrosamine analogs (MNP and CPNP) originate in the drug synthesis process. (26) | rifampin and rifapentine |

**Daily Intake of Nitrosamine**

| Nitrosamine | AI Limit (ng/day) |
|---|---|
| NDMA | 96 |
| NDEA | 26 |
| NMBA | 96 |
| NMPA | 26 |
| NIPEA | 26.5 |
| NDIPA | 26.5 (27) |

**Methods to detect the Nitrosamine.**

They are many Analytical Methods for Determining Nitrosamines (NAs) Non chromatographic Methods, Liquid Chromatographic methods (HPLC), and non-Chromatographic methods. They are many samples Preparation methods Distillation, Solid phase Extraction (SPE), Direct Liquid Extraction (DLE), Liquid- Liquid Extraction (LLE). (28) Various alternatives methods of analysis for nitrosamine assessment in water samples have been examined, including LC-UV identification, (29,30) chemiluminescence (CL) in combination with LC-

UV, (31,32) high-field asymmetric wave form ion-mobility spectrometry (FAIMS)-MS (33), including HPLC-ion exclusion-UV-vis (34). Only CL-LC-UV and FAIMS-MS have been demonstrated to identify nitrosamines in drinking water at low ng/L levels, up to 10ng/L (34,32). In Eiichi Yamamoto et al used SPE LC-APCI-MS\MS method the liquid chromatography separations were carried out on a Nexera LC-40 ultra-high performance liquid chromatography machine. The approach allows for the accurate, precise, and sensitive assessment of NDMA levels in model medicines ranging from sub-ng/mL to 100 ng/mL (0.038-15.0 ppm for metformin hydrochloride and 0.042-8.33 ppm for ranitidine hydrochloride). The technology could be used to analyze trace NDMA in a variety of medications (35). In GC-MS/MS Method for Trace Level Quantification of Six Nitrosamine Impurities (NDMA, NDEA, NEIPA, NDIPA, NDPA, and NDBA) in Commercially Used Organic Solvents: Dichloromethane, Ethyl Acetate, Toluene, and O-xylene) Method Validation was done of GC- MS\MS. The validated method was used to evaluate commercial samples of dichloromethane, ethyl acetate, toluene, and o-xylene. According to the findings, toluene was contaminated with NDEA (550 ppb), whereas o-xylene was contaminated with NDEA (120 ppb) and NDBA (3400 ppb) (36). The Approximate NA limit in the sample should be 0.03 % for detection. Kartheek Srinivas Chidella et al has performed LC MS\MS analytical technique for detection of six NAs in Telmisartan. The estimated LOQ and LOD readings are extremely low, demonstrating the method's sensitivity. The validated method can be used to routinely quantify all six nitrosamine impurities in telmisartan at 1.5 ppb concentration. When compared to other detection techniques, such as GC-MS/MS, which have limitations in ionising impurities such as NMBA contaminant, the LC-MS/MS methodology allowed us to quantify a greater number of impurities (37) In Mikhail Khorolskiy et al Valsartan, Losartan, and Irbesartan model combinations were evaluated with nitrosamine concentrations of 0.2, 0.4, 0.6, 0.8, and 1.1 ng/mL, respectively, to determine the limit of detection (LOD) for the established method. A signal-to-noise (S/N) ratio of 3 was the major acceptance requirement for the detection limit. Experiments aided in determining the method's detection limit of 0.2 ng/mL. The mean S/N ratio obtained from three successive observations at this concentration was 3.7. The method's limit of quantification was determined by analyzing model mixes with concentrations of 0.2, 0.4, 0.6, 0.8, and 1.1 ng/mL (38). The entire work-up strategy is divided into three steps. The first step is to extract the NA with an appropriate solvent that can dissolve NA but not the API. The second stage is to remove substances with alkaline characteristics using strong cation exchange resins. The final stage is to enrich NA with active charcoal, which is also used in the field of environmental and water analysis. According to a limit of 26.5 and 96 ng/day for NDEA and NDMA, the upper limit values for a single daily supplied 500 mg placebo tablet are 0.053 ppm NDEA and 0.192 ppm NDMA (39). The working group took an alternative strategy, leveraging the distinct capabilities of super-critical fluid chromatography (SFC) combined with tandem mass spectrometry (MS/MS). This was the first method to combine the analysis of a large set of ten different NAs with the purity testing of the legally mono-graphed impurities and associated substances of the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.). (40) The method was created using the ICH Q8's holistic Quality-by-Design (QbD) philosophy, validated for limit testing using ICHQ2, and referred to as a "rather new approach with advantages for routine analysis" in the EMA's provisional final declaration on nitrosamine impurities in June 2020. (41)

## CONCLUSION:

Nitrosamines are Potent carcinogens whose exposure through food, beverages, and, more recently, pharmaceuticals must be regulated and minimized. The everyday diet of nitrosamine contamination has limits and acceptance. Nitrosamines may interfere with finished pharmaceutical products during API synthesis & formulations manufacture. Nitrosamine contamination from API synthesis can be reduced or eliminated by changing synthesis techniques and making sure solvent & reagents remain free from contamination. When evaluating excipients that form nitrosamine precursors, and evaluating formulations stability and the nitrosamine migration through packaging and printing procedures can reduce formulating side taint of the final products. The analytical approach for determining and quantifying Nitrosamine impurities is GC or LC utilizing mass spectroscopy. To determine these contaminants at very low levels, these procedures must be thoroughly designed and validated in accordance with ICH requirements. Health Canada has issued multiple public notices to manufacturers to help them control and limit these contaminants to appropriate ingestion levels.

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**Conflict of Interest:**

The Authors declare no conflict of interest

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