A Review on Synthesis and Biological Activities of Nitrosamine Impurities in Active Pharmaceutical Ingredients (APIs)

Pooja S Dalvi[1], Sharad S Sankhe[2]

[1]Ph.D. Scholar, Department of Chemistry, Patkar-Varde College, Goregaon West, Mumbai-61, India

[2]Head of Department, Department of Chemistry, Patkar-Varde College, Goregaon West, Mumbai-61, India

DOI: https://doi.org/10.51244/IJRSI.2025.120800343

Received: 05 September 2025; Accepted 11 September 2025; Published: 13 October 2025

ABSTRACT

Nitrosamine impurities are chemical compounds that can unintentionally form in active pharmaceutical ingredient during manufacturing or storage. Nitrosamine are carcinogenic and genotoxic. Nitrosamines are a group of nitroso compounds that can be formed when secondary or tertiary amine from API like-Lansoprazole, Dasatinib, Nilotinib or Oxybutynin react with nitrosating agents like $NaNO_2$ in acidic medium or Tert-butyl nitrite etc. Validated analytical methods are used for identification and quantification these impurities. Highly sensitive instruments like High performance liquid chromatography (HPLC) and Gas chromatography (GC) required for quantification of these impurities and Mass Spectroscopy (MS) and Nuclear Magnetic Resonance (NMR) are required for identification, these impurities have certain limit which can be detected on these instruments.

Keywords: Nitrosamine impurities[1], Drug substances[2], Classifications[3], Drug product[4], Impurities[5], Impurity synthesis[6].

INTRODUCTION

Nitrosamine impurities can be formed during formation and degradation of active pharmaceutical ingredients. They can be formed by use of nitrosating agent, cross-contamination, solvent contamination, amines in raw material and degradation. Nitrosamine has carcinogenic, genotoxic and mutagenic properties; very small exposure to nitrosamines can lead to cancer. Regulatory agencies such as health Canada and FDA have established acceptable intake limit for commonly identified nitrosamines in pharmaceuticals to minimize potential carcinogenic risk shown in Table 2.

In July 2018 FDA (Food and Drug Administration) and EMA (European Medicines Agency) announced that N-Nitroso dimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) are carcinogenic impurities detected in generic substances and drug product especially in Sartans class Angiotensin II receptor (AT_1R) blockers like Valsartan, losartan, Irbesartan, Candesartan, Azilsartan etc. which is used to treat Hypertension (High Blood Pressure) and Heart failure in patients.

ICH M7 (Mutagenic impurity management expectations) classified nitrosamine impurities as Class 1 impurity and known as carcinogenic and mutagenic based on their carcinogenicity and mutagenicity. Nitrosamines impact the pharmaceutical material by mutation through rearrangement, chromosomal breaks or insertion into the DNA during replication. Nitrosamine impurities even very low concentration in drug can cause cancer so identification and quantification of these impurities is very important.

A Review On Synthesis And Biological Activities Of Nitrosamine Impurities

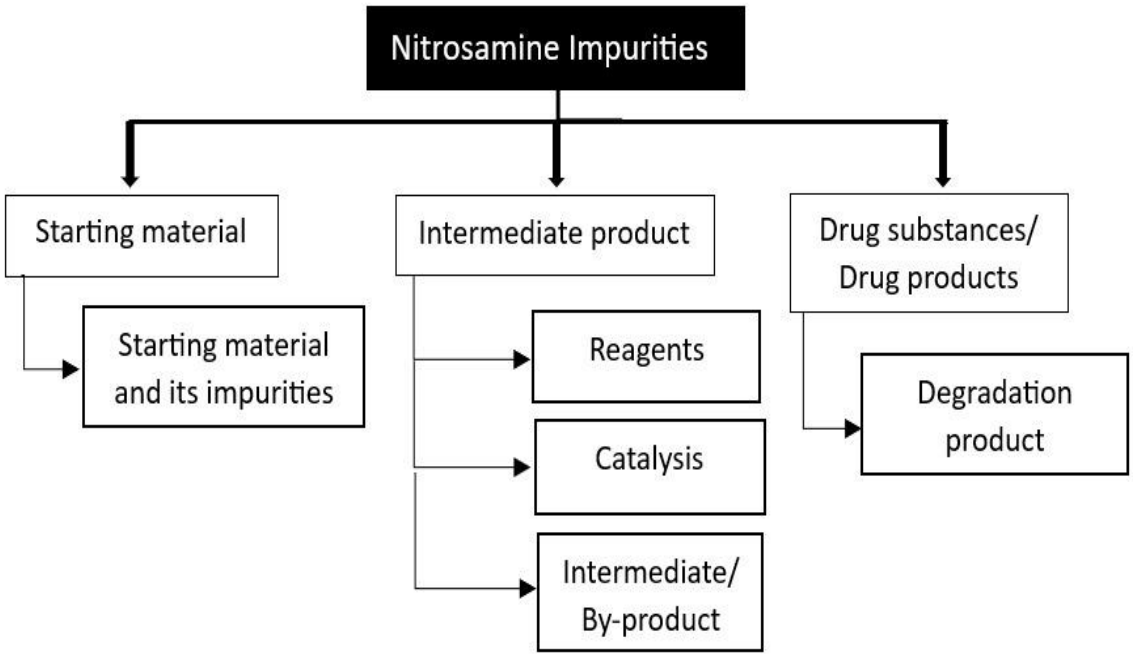
1. Sources of Nitrosamine Impurities

Impurities can be generated during formulation or degradation of active pharmaceutical ingredient. The possible routes of nitrosamine formation in active pharmaceutical ingredients (APIs) shown in Fig.1. In process nitrosamines can be generated due to impure starting material, residual solvents, reuse of catalyst, degradation of active pharmaceutical ingredients at high temperature or due to moisture in storage. Nitrosamine can be

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue IX September 2025

formed during packaging when rubber stopper or nitrocellulose coating react with amine from active pharmaceutical ingredients. Light exposure can lead to nitrosation in sensitive active pharmaceutical ingredients.

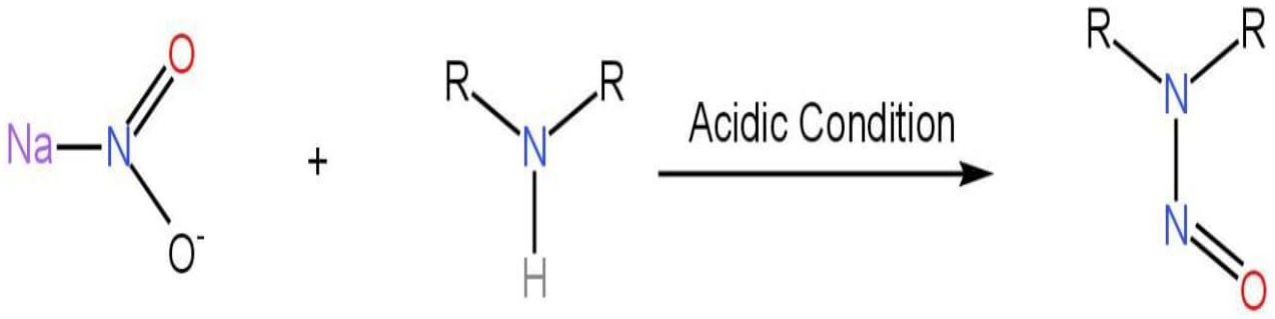
Figure 1 Sources of Nitrosamine Impurities



2. Formation of Nitrosamine impurities

When primary amine, secondary amine, tertiary amines or quaternary ammonium salts in acidic or thermal condition react with nitrosating agents like Sodium nitrite or p-Toluene sulphonic acid are considered to be precursors for the generation of Nitrosamine impurities as shown in Fig.2. During degradation of API in some pharmaceutical ingredients containing diethyl amino, dimethyl amino, etc. can break down to free amine which can react with nitrite during packaging.

Figure 2 General Reaction of Nitrosamine Formation



For example:

At room temperature when diethyl amine in acidic condition treated with sodium nitrite yields N-Nitroso diethyl amine as shown below:

$$(C_2H_5)_2NH + NaNO_2 + HCl \longrightarrow (C_2H_5)_2N\text{-}NO + NaCl + H_2O$$

Diethylamine — N-Nitrosodiethylamine

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue IX September 2025

Recovered solvents, raw materials and catalysts used in the synthesis may cause risk for Nitrosamine formation during synthesis. Contaminated raw material or starting material may introduce the Nitrosamine impurities formation in active pharmaceutical ingredients or drug product. In manufacturing process where nitrosating agents are not intentionally used may be contaminated through nitrite present in the water used for process.

The U.S. FDA has recognized several common nitrosamines that have raised safety concerns in pharmaceuticals due to their potential carcinogenicity. Impurities in Table 2 shows commonly detected in various drug classes including Sartans, ranitidine, metformin, etc.

Intake limit of nitrosamine varies depending on type of nitrosamine as shown in Table 2. Nitrosamine are class of compounds and several of them are probable human carcinogens such as NDMD, NDEA, NMBA etc. so the limit is extremely low based on lifetime cancer risk.

According to European Food Safety Authority (EFSA), exposure to nitrosamine poses significant health risk for individual for all age group. Nitrosamine formation observed in food at certain condition such as high temperature during cooking, flavouring agents, fermentation, etc. as shown in Table 1 which increased risk of cancer and genotoxicity in human being and animals.

3. Comparative interpretation of commonly identified Nitrosamines

FDA had classified nitrosamine depending on its Carcinogenic Potency Categorization Approach (CPCA) into following class:

a) Category 1 - Highest potency - Lowest acceptable limit (≈18 ng/day)

b) Category 2 & 3 - Intermediate potency - Moderate acceptable limit (≈ 36-100 ng/day)

c) Category 4 - Lower potency - Higher acceptable limit (≈ 500 ng/day)

d) Category 5 - Lowest potency - Highest acceptable limit (≈ 1500 ng/day)

Carcinogenic Potency Categorization Approach assigns nitrosamine to category based on their predicted carcinogenic risk, which can be done by analysing α-Hydrogens, Activating features, Deactivating features.

a) α-Hydrogens

It is a Hydrogen atom which is directly bonded to the carbon atom adjacent to a carbonyl group (C=O)

b) Activating features

It increases the carcinogenic potential of nitrosamine by promoting metabolite activation especially by α-Hydrogenation, Benzyl group, Electron-donating groups, Alkyl chains, etc.

c) Deactivating features

It reduces the carcinogenic potential of nitrosamine by hindering metabolite activation especially by Carboxylic acid groups, Electron-withdrawing groups, Steric hindrance, etc.

These features are used in a scoring system called “CGPA” where:

Potency Score = α-Hydrogen Score + Activating feature Score + Deactivating feature Score

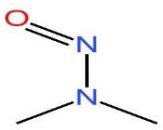
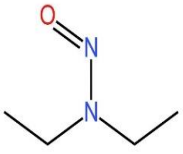
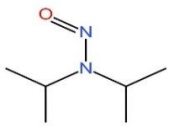
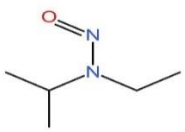
- Higher Potency Score indicates Lower carcinogenic potency
- Lower Potency Score indicates Higher carcinogenic potency

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue IX September 2025

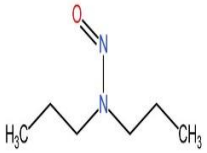
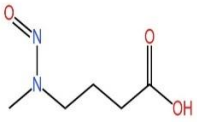
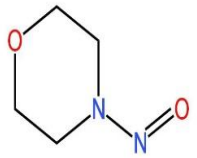
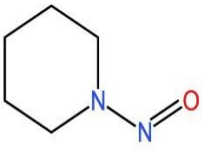
Table 1 Common nitrosamines found in Food in certain condition are as follow

Nitrosamine	Food Type
1. NDMA	Cured meat – Frying bacon Smoked meat/fish – Smoking process Beer – During malt drying Cheese – Bacterial activity Soy sauce, Fish Souse – Fermentation and aging Pickled vegetables - Fermentation Instant noodles – Spices and preservatives Garlic food -High heating grilling
2. NDEA	Cured meat – Frying bacon
3. NDIPA	Cooked sausage and ham – High temperature
4. NEIPA	Cured meat – Grilling, Frying bacon
5. NDPA	Cured meat – bacon and oath
6. NMOR	Curded meat, Fish – Nitrite treated food
7. NPYR	Pickled Vegetable, salted fish – presence of nitrite & precursor

Table 2 Structure of commonly identified Nitrosamine impurities and its biological activities with Intake Limit

Amines	**Corresponding Nitrosamine Impurity Name & Acronym**	**Stucture**	**Biological Activities on Organ**	**Intake Limit (in nanograms)**
Dimethyl amine	NDMA (N-Nitroso dimethylamine)		Liver, Lung, Kidney, DNA	26.5 ng/day
Diethyl amine	NDEA (N-Nitroso diethylamine)		Liver, Oesophagus, Respiratory track, DNA damage,	26.5 ng/day
Diisopropylamine	NDIPA (N-Nitroso diisopropylamine)		Lung, Pancreas, Enzyme, Respiratory and Systemic toxicity	26.5 ng/day
Ethylisopropylamine	NEIPA (N-Nitroso ethylisopropylamine)		Lungs, Urinary bladder, Colon, Kidneys, Nasal cavity, Pancreas, Stomach and Central nervous system	400 ng/day

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue IX September 2025

Dipropylamine	NDPA (N-Nitroso dipropylamine)		Liver, Oesophagus, Nasal cavity, DNA damage	26.5 ng/day
N-methylamino-butyric acid	NMBA (N-Nitroso-N-methyl aminobutyric acid)		Oesophagus, Liver, Lung, Kidney, Stomach and intestine	1,500 ng/day
Morpholine	NMOR (N-Nitroso morpholine)		Oesophagus, Nasal cavity, Lungs	Not Available
Piperidone	NPYR N-Nitroso Piperidone		Liver, Oesophagus, Nasal cavity, Lungs	Not Available

DISCUSSION

In the article "Nitrosamine Impurities in Drug Substances and Drug Products''[1] the researchers concentrated how nitrosamine impurities get generated during formulation and degradation of any active pharmaceutical ingredient (API), sources of nitrosamine impurities, regulatory perspective by Food and Drug Administration (FDA) European Medicines Agency (EMA) and other regulatory agencies like Therapeutic Goods Administration (TGA), and described acceptable intake limit of nitrosamine content containing drugs, and how to avoid nitrosamine contamination.

In the article by Antonis Manolis (April 26, 2019), "Carcinogenic Impurities in Generic Sartans: An Issue of Authorities' Control or a Problem with Generics",[2] researchers recalled Sartans generics like Valsartan, Irbesartan, Losartan in which nitrosamine impurities generated and companies involved. Studies have shown that NMBA is known to be a co-carcinogen in animal which can cause bladder cancer in rats which renders its potential in human carcinogen.

Jennifer L. Caulfield's 1997 doctoral dissertation, titled ''The chemistry of nitric oxide-induced deamination and cross-linking of DNA'',[3] explores the chemical reactions between nitric oxide and DNA resulting structural and functional consequences for DNA, specifically focusing on how nitric oxide can cause deamination and cross-linking of DNA. In the context of DNA deamination can alter the pairing properties of nucleotides which potentially leading to mutation.

The article, ''The molecular basis for induction of human cancers by tobacco specific nitrosamine' by R. Nilsson (July, 2011)'',[4] explores the link between cancer development and tobacco-specific nitrosamines (TSNAs), specifically focusing on how nitrosamine compounds damage DNA. Cellular DNA damage if not repaired, it can lead to cancer development. An exposure level of TSNA does not increase the baseline levels of DNA damage which can be considered as virtually safe.

In the paper, by Lijinsky William & Andrews A. W. October 1983, "The superiority of hamster liver microsomal fraction for activating nitrosamines to mutagens in Salmonella typhimurium",[5] investigated the mutagenic activation of nitrosamine nitrosamines by hamster liver microsomal fractions in Salmonella typhimurium, the study also noted that nitrosamines activated by hamster liver microsomes showed a tendency to be more

carcinogenic in hamsters than in rats. Some nitrosamine impurities were found to be very potent mutagens when activated by hamster liver.

In the article, ‘‘U. S. Food and Drug Administration update (Jan 25, 2019), “Statement on the FDA’s ongoing investigation into valsartan and ARB class impurities and the agency’s steps to address the root causes of the safety issues”,[6] The FDA was actively investigated the presence of nitrosamine impurities in valsartan and other ARB medications The agency was working to understand how these impurities were forming during the manufacturing process. The FDA also reported recalls of certain valsartan, losartan, and irbesartan products due to the presence of impurities.

In the article, by G. Subba Rao (1980), “N-Nitrosamines from drugs and nitrite: potential source of chemical carcinogens in humans”, Pharmacy International, Volume 1’’,[7] drug-drug interactions may lead to nitrosamine formation thus organic ester vasodilator drugs when ingested with propranolol a secondary amino anti-arrhythmic drug yields as N-Nitroso propranolol, a tertiary amino tranquilizer drug, form the N-nitroso piperazine.

In the article, “U.S. Food & Drug Administration. 2019. FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall”, [17] research concentrated on nitrosamine impurities formed during synthesis Afatinib at laboratory scale, and MRM transitions used for quantification and identification of N-Nitrosodimethylamine (NDMA)and internal standard NDMA-d6, standard process for analysis of traces of NDMA in tablet.

In the paper, “Genotoxicity of glycidamide in comparison to (l)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10 epoxide and a-acetoxy-N-nitroso-diethanolamine in human blood and in mammalian V79-cell”, [21] the researcher concentrated on genotoxic and neurotoxic activity of glycidamide in comparison to known carcinogens (l)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10 epoxide and a-acetoxy-N-nitroso-diethanolamine. GA induced DNA damage in human blood in concentration dependent manner.

In the paper, “Nitrosamine Contamination in Pharmaceuticals: A Comprehensive Review on Nitrosation Pathways, Potential Root Cause, Detection, Risk Assessment, and Mitigation Strategies”,[22] the researchers concentrated on formation of nitrosamine in active pharmaceuticals like - ARBs, Anti-diabetic, Histamine-2 receptor, Anti- microbial and other during process and contamination. Nitrosamine formation pathway between nitrosating agent and primary, secondary, tertiary and quaternary ammonium amines under certain conditions.

In the paper, “An update on the current status and prospects of nitrosation pathways and possible root causes of nitrosamine formation in various pharmaceuticals”, [23] researchers concentrated on classification of nitrosamine based on their carcinogenic potential and possible roots causes contamination in active pharmaceutical ingredients like Sartans, Histamine-2 (H_2) receptor antagonists, Antidiabetic agents, Anti-microbial agents, etc., and have explained Acceptable Limit of commonly identified nitrosamines.

In a paper, “Analytical Methodologies to Detect N-Nitrosamine Impurities in Active Pharmaceutical Ingredients, Drug Products and Other Matrices’’,[25] researcher concentrated on Availability of analytical methods, toxicological data, list of nitrosamines and their limits, and explained main sources of nitrosamine through which human is exposed to these impurities which include food such as cooked/fried meat, vegetable, spiced food, cocoa, beer, fats, oils, treated water, tobacco, pharmaceutical products, air pollution, personal care products and cosmetic, etc.

CONCLUSION

The synthesis of nitrosamine impurities plays an important role in modern research. Nitrosamine impurities are highly mutagenic and carcinogenic need acceptable limit in drugs and drug products. Potential sources of nitrosamine impurities such as raw material, reagents, solvents, catalysts, cross-contamination, degradation product, etc. Nitrosamine impurities need to be identified to control it in drug product and drug substance. Impurity synthesis can be avoided by selecting pure and proper reagents, solvents and catalysis during synthesis of drug substances. The analytical methods such as HPLC, Mass, NMR, GC are used for identification and

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue IX September 2025

quantification of impurities. The available research data point out possibility of carcinogenic nitrosamine formation in humans from drug-nitrite interactions.

Sartans recall due to carcinogenic impurities, detected in large numbers, continue to raise concerns about the reliability of the generic drug industry. However, there is still problem with these generic, two of these are pseudo generics and carcinogenic impurities (NDMA) were detected and recall, NDMA contaminated generic is valsartan.

The chemical interactions between nitric oxide and DNA can cause deamination and cross-linkage of DNA. A chemical reaction where an amine group ($-NH_2$) is removed from a molecule, the context of DNA determination alters the base pairing properties.

The study link between tobacco-specific nitrosamines (TSNAs) and cancer development, specifically focusing on how these compounds damage DNA, TSNA forms adduct with DNA it means they attach to DNA strands, potentially disrupting normal function of DNA. If DNA damage is not repaired in time, it can initiate cancer. Further study found that the level of TSNA inducted DNA damage in individuals using low nitrosamine oral snuff product indicating low risk of cancer from these products.

The study focused on the role of liver microsomal fractions in the metabolic activation of nitrosamines. Microsomes, derived from the endoplasmic reticulum, contain enzymes like cytochrome P450s that can metabolize xenobiotics, including nitrosamines. The research indicated that hamster liver microsomes were particularly efficient in activating a range of nitrosamines to mutagens compared to other liver preparations. The metabolic activation of nitrosamines, particularly by hamster liver, plays a crucial role in their mutagenic and potentially carcinogenic effects.

Nitrosamines are a class of compounds that are considered probable human carcinogens. Their presence in medications has raised significant concerns, leading to recalls and regulatory action. The FDA has been working with manufacturers to identify and address the sources of these impurities and to implement preventative measures. The FDA was taking steps to mitigate the risks associated with these impurities and ensure the safety of medications for patients. The agency was working to understand how these impurities were forming during the manufacturing process.

The organic nitrate drugs generate nitrite ions under acidic condition found in the human stomach which then react with secondary or tertiary amino drugs to yield nitrosamines. All new drugs containing secondary and tertiary amino groups should be evaluated for nitrosative toxification by nitrite. Nitrate and nitrite are extensively used as fertilizers in agriculture, colour and flavour enhancer in processed food.

Nitrosamine represent a significant class of pharmaceutical and environmental contaminants with well-established carcinogenic properties. Their synthesis occurs through multiple pathways. The recent detection of nitrosamine impurities in pharmaceuticals has highlighted the need for comprehensive understanding of their formation, detection, and control. Future research should focus on developing more sensitive analytical methods, better understanding tissue-specific effects, and implementing effective prevention strategies.

Supplier qualification and Row material testing can reduce nitrosamine formation possibility during process. Nitrite scavengers such as Ascorbic acid, alpha-tocopherol and amino acids can be used to prevents nitrosamine formation. Nitroso reactions are pH dependent so adjusting pH of final product to basic or neutral can prevent degradation of API to Nitroso compound. Avoid use of recycled solvents or by testing make sure that recycled solvents are nitrosamine free.

REFERENCE

1. Shaikh, Tabrez, Gosar, Amit & Sayyed, Hussain (January 2020), 'Nitrosamine Impurities in Drug Substances and Drug Products', Journal of Advances in Pharmacy Practices. https://doi.org/10.5281/zenodo.3629095

2. Manolis, Antonis (26 April 2019), 'Carcinogenic Impurities in Generic Sartans: An Issue of Authorities' Control or a Problem with Generics', Rhythmos, vol. 14, no. 2, pp. 23–26.
3. Caulfield, Jennifer 1997, 'The chemistry of nitric oxide-induced deamination and cross-linking of DNA', Massachusetts Institute of Technology, pp. 1–153.
4. Nilsson R. (July 2011), 'The molecular basis for induction of human cancers by tobacco specific nitrosamines', Regulatory Toxicology and Pharmacology, vol. 60, no. 2, pp. 268– 280.
5. Lijinsky William & Andrews A. W., (October 1983), 'Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis', vol. 111, no. 2, pp. 268–280, https://doi.org/10.1016/0027-5107(83)90058-1
6. 25 Jan 2019, 'Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues', U. S. Food and Drug Administration update, https://www.fda.gov
7. Rao Subba G., (1980), 'N-Nitrosamines from drugs and nitrite: potential source of chemical carcinogens in humans', Pharmacy International, vol. 1, pp. 187–190.
8. Douglass, et al 1973, 'The chemistry of Nitrosamine Formation: relevance to malting and brewing', J Soc. Cosmit. Chem.
9. Beard Jessica C. & Swage Timonthy M. (2021), 'An Organic Chemist's Guide to N-Nitrosamines: Their Structure, Reactivity, and Role as Contaminants', J. Org. Chem, pp. 86,2037–2057.
10. Dande Aishwarya, Dhampalwar Vaishnavi, Ramakant Pallaprolu Nikhil & Peraman, Ramalingam. (November 2020), 'nitrosamine Impurities in Medicines: Toxicity, Formation Pathways, Methods of Determination, and Limits'. https://doi.org/10.33380/2305-2066-2020-9-4-180-190
11. Cioc Razvan C., Joyce, Ciaran Mayr Monika & Bream Robert N. (July 2023), 'Formation of N-Nitrosamine Drug Substance Related Impurities in Medicines: A Regulatory Perspective on Risk Factors and Mitigation Strategies'.
12. Dande, Aishwarya, Dhampalwar, Vaishnavi, Ramakant, Pallaprolu, Nikhil & Peraman, Ramalingam. (April 2025), 'Nitrosamine Drug Substance-Related Impurities (NDSRIs) in Pharmaceuticals: Formation, Mitigation Strategies, and Emphasis on Mutagenicity Risks', https://doi.org/10.1007/s11095-025-03857-9
13. Ashworth Ian W., Blanazs Alexander, Byrne Jonathan J., Dirat Olivier, Fennell Jared W., Kuhl Nadine, ... Whiting Matthew P. (2023), 'Approaches and Considerations for the Investigation and Synthesis of N-Nitrosamine Drug Substance-Related Impurities (NDSRIs)'. https://pubs.acs.org/doi/10.1021/acs.oprd.3d00084
14. Andrews A.W., Lijinsky W., & Snyder S.W. (1996). 'Metabolic activation and DNA interactions of carcinogenic N-nitrosamines. Environmental Health Perspectives', pp-104, 1075-1082.
15. Barceloux, D.G. (2012). 'N-Nitrosamines. In Medical Toxicology of Natural Substances'. pp. 127-134.
16. John Wiley & Sons Billet S., et al. (2023). 'DNA alkylation damage by nitrosamines and relevant DNA repair pathways. International Journal of Molecular Sciences', 24(5), 4684.
17. U.S. Food & Drug Administration. (2019). 'FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall'. https:// www.fda.gov/news-events/press
18. Eisenbrand G. (2020). 'Revisiting the evidence for genotoxicity of acrylamide (AA), key food process contaminant'. Archives of Toxicology, 94(12), 4113-4147.
19. Beard Jessica C., Timothy M. Swager (ed.), (2021), 'An Organic Chemist's Guide to N-Nitrosamines: Their Structure, Reactivity, and Role as Contaminants', The Journal of Organic Chemistry, pp. 86,2037–2057. https://pubs.acs.org/doi/10.1021/acs.joc.0c02774
20. Meadows Maxwell, Soni M. Pradhanang, Thomas B. Boving & Hichem Hadjeres (eds), (2019), 'Nitrosamines: A review of formation pathways, precursors, control, and occurrence in drinking water', MATEC, University of Rhode Island. https://doi.org/10.1051/matecconf/201928005003
21. Thielen Silke n.d., Matthias Baum, Michelle Hoffmann, Richard N. Loeppky & Gerhard Eisenbrand (eds), 'Genotoxicity of glycidamide in comparison to (l)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10 epoxide and a-acetoxy-N-nitroso-diethanolamine in human blood and in mammalianV79-cell', Department of Food Chemistry and Environmental Toxicology, University of Kaiserslautern, Germany. https://doi.org/10.1002/mnfr.200500227
22. Ukhade Snehal, Sandeep Sonawane (ed.), (September 2024) 'Nitrosamine Contamination in Pharmaceuticals: A Comprehensive Review on Nitrosation Pathways, Potential Root Cause, Detection, Risk

Assessment, and Mitigation Strategies', 21st edition, Bioscience Biotechnology Research Asia, pp. 893–911. http://dx.doi.org/10.13005/bbra/3272

23. Wichitnithad Wisut, Siriwan Namtaphol, Kachathong Noppakhunsomboon & Pornchai Rojisittisak (eds), (2023). 'An update on the current status and prospects of nitrosation pathways and possible root causes of nitrosamine formation in various pharmaceuticals', Saudi Pharmaceutical Journal, Thailand, pp. 295–311. https://doi.org/10.1016/j.jsps.2022.12.010
24. Moser Justin, Ashworth Ian K., Harris Laurence, Hillier Michael C., Nanda Kausik K., & Scrivens Garry. (May 2023), "N-Nitrosamine Formation in Pharmaceutical Solid Drug Products: Experimental Observations", Journal of Pharmaceutical Science. Vol. 112, 5. pp. 1255-1267.
25. https://doi.org/10.1016/j.xphs.2023.01.027
26. Manchuri Krishna M., Shaikh Mahammad Ali, Reddy Gopireddy, Venkata Sultana S., Naziya, & Gogineni Sreenivasarao, (2024), 'Analytical Methodologies to Detect N-Nitrosamine Impurities in Active Pharmaceutical Ingredients, Drug Products and Other Matrices', Chemical Research in Toxicity. pp. 1456-1483. https://doi.org/10.1021/acs.chemrestox.4c0023
27. Golob Nejc, Peterlin Simona, Grehek Rok, Roskar Robert, (2023), 'NDMA Formation Due to Active Ingredient Degradation and Nitrite Traces in Drug Product', Journal of Pharmaceutical Science. https://doi.org/10.1016/j.xphs.2023.01.021