Indian Journal of Health Care, Medical & Pharmacy Practice (Vol 7, Issue 2, July-December 2026)
Home page of the journal: https://ijhmp.com/Home

Review Article

A COMPREHENSIVE REVIEW ON RANITIDINE-ASSOCIATED NDMA CONTAMINATION AND CANCER RISK

Mr. Anand Kumar Gupta[1*], Naziya Parveen[2], Ridhima Kumari[3], Varun Kumar[4], Saurabh Verma[5]

[1,3,4,5]Department of Pharmaceutical Chemistry, SNS College of Pharmacy Motihari, Bihar, India.
[2]Divine College of Pharmacy Ziradei, Siwan, Bihar, India.

Corresponding Author*: Mr. Anand Kumar Gupta, Assistant Professor, Department of Pharmaceutical Chemistry, SNS College of Pharmacy Motihari, Bihar, India.

Email ID: anandbpharma4@gmail.com

DOI: https://doi.org/10.59551/IJHMP/25832069/2026.7.2.139

How to cite this article: Gupta AK, Praveen Z, Kumari R et al. A Comprehensive Review on Ranitidine-Associated NDMA Contamination and Cancer Risk. *Indian J. Health Care, Med. Pharm. Pract.* 2026;7(2):249-256.

COPYRIGHT@ 2026, IJHMP | This work is licensed under a Creative Commons Attribution 4.0 International Licence

Received: 20 July, 2026, Decision for Acceptance: 24 Aug, 2026

ABSTRACT

Background: Ranitidine is a widely used histamine H_2-receptor antagonist (H_2RA) indicated for the management of gastroesophageal reflux disease (GERD), peptic ulcer disease, and other acid-related gastrointestinal disorders. In 2019, the detection of N-nitrosodimethylamine (NDMA), a probable human carcinogen classified by the International Agency for Research on Cancer (IARC Group 2A), in certain ranitidine formulations raised significant concerns regarding drug quality and patient safety. Subsequent investigations demonstrated that NDMA concentrations may increase during manufacturing, storage, and exposure to elevated temperatures, resulting in global regulatory actions, including the withdrawal or suspension of ranitidine products in several countries.

Objective: This review summarizes the current scientific evidence on NDMA contamination in ranitidine, including its mechanisms of formation, toxicological effects, analytical detection, regulatory responses, and the available evidence regarding cancer risk.

Methods: A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, together with official reports from the FDA, EMA, WHO, and IARC. Peer-reviewed articles and regulatory documents published between 2018 and 2026 were critically evaluated according to predefined eligibility criteria.

Results: Available evidence indicates that NDMA formation in ranitidine is influenced by molecular instability, manufacturing conditions, storage duration, and elevated temperatures. Experimental studies consistently demonstrate the genotoxic potential of NDMA through DNA alkylation, oxidative stress, and mutagenic mechanisms. However, epidemiological studies have reported inconsistent findings, and current evidence does not establish a definitive causal association between therapeutic ranitidine use and current evidence is insufficient to confirm that therapeutic ranitidine exposure contributes to cancer development.

Conclusion: NDMA Contamination Represents a Significant Pharmaceutical Quality Concern Requiring Stringent Impurity Monitoring and Regulatory Oversight. Further multicentre epidemiological studies, standardized analytical methods, and improved pharmacovigilance are essential to clarify the long-term health implications to better understand the long-term health consequences associated with NDMA exposure while supporting the development of safer and higher-quality pharmaceutical therapies.

KEYWORDS: Ranitidine, N-nitrosodimethylamine (NDMA), Histamine H_2-receptor Antagonist, Cancer Risk, Nitrosamine Impurities, Drug Safety, Pharmacovigilance, Toxicology, Regulatory Affairs.

Introduction

Ranitidine belongs to the class of histamine H_2-receptor antagonists (H_2RAs) and was extensively prescribed for the management of various disorders associated with excessive gastric acid secretion, such as gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), Zollinger–Ellison syndrome, and functional dyspepsia. Its therapeutic effect is achieved through competitive inhibition of histamine H_2 receptors on gastric parietal cells, thereby suppressing both basal and stimulated gastric acid secretion. Because of its proven clinical effectiveness, low cost, and acceptable tolerability, ranitidine remained one of the most frequently prescribed anti-secretory medications for several decades[1-4].

Table 1: Basic pharmacological profile of ranitidine

Parameter	Description
Drug Class	H_2 receptor blocker used to decrease stomach acid
Mechanism	Inhibits H_2 receptors and lowers gastric acid secretion
Indications	GERD, PUD, Zollinger–Ellison syndrome, Dyspepsia
Routes	Oral, IV, IM
Market Status	Withdrawn in many countries because of NDMA concerns

A major safety concern emerged in 2019 when NDMA was identified in multiple ranitidine formulations. NDMA, a nitrosamine impurity recognized by the International Agency for Research on Cancer (IARC) as a Group 2A (probably carcinogenic to humans) substance, attracted global regulatory attention. Further investigations indicated that the amount of NDMA could increase under certain manufacturing conditions, prolonged storage, or exposure to elevated temperatures, highlighting important issues related to medicine quality and patient safety[3-6].

Table 2: Regulatory Timeline

Year	Event
2019	NDMA detected in ranitidine
2019	FDA initiated investigation
2020	FDA requested market withdrawal
2020	EMA suspended ranitidine medicines
2020	MHRA and CDSCO issued safety actions

NDMA is metabolized by CYP2E1 into reactive intermediates that cause DNA alkylation, oxidative stress, and genetic mutations, which may contribute to carcinogenesis. While animal studies demonstrate the carcinogenic potential of NDMA, epidemiological studies in humans have shown inconsistent findings regarding cancer risk associated with ranitidine use[5,7-10].

Table 3: International Organizations

Organization	Role
FDA	Drug safety and product recall
EMA	Regulatory evaluation
WHO	Public health guidance
IARC	Carcinogen classification
CDSCO	Drug regulation in India

This review summarizes the current evidence on NDMA contamination in ranitidine, including its formation, toxicological mechanisms, cancer risk, analytical detection, and global regulatory actions, highlighting their implications for pharmaceutical quality and patient safety[1-10].

Materials and Methods

A comprehensive literature search was conducted to identify relevant studies related to ranitidine pharmacology, NDMA contamination, toxicological effects, cancer risk, and regulatory actions. The review was prepared according to the principles of systematic literature evaluation and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Databases

Scientific articles and regulatory documents were collected from major biomedical databases and official regulatory websites, including PubMed, Scopus, ScienceDirect, Google Scholar, WHO, FDA, and EMA databases.

Search Strategy

The literature search was performed using combinations of keywords such as:

"Ranitidine", "NDMA contamination", "N-nitrosodimethylamine", "ranitidine degradation", "carcinogenic risk", "drug withdrawal", and "regulatory action".

Studies published mainly between 2018 and 2026 were considered to include recent evidence regarding NDMA contamination and regulatory updates.

Inclusion Criteria

Studies were selected based on the following criteria:

- Research articles related to ranitidine and NDMA formation
- Toxicological and carcinogenicity studies
- Regulatory reports from recognized agencies
- Studies published in English language
- Publications from 2018–2026

Exclusion Criteria

Studies were excluded if they included:

- Duplicate publications
- Non-scientific articles
- Unrelated drug impurity studies

- Articles without sufficient data
- Non-English publications

Study Selection: Initially, identified records were screened through titles and abstracts. Relevant studies were further evaluated by full-text assessment. Studies fulfilling the eligibility criteria were included for qualitative analysis.

PRISMA Statement: The study selection process followed PRISMA guidelines, involving four major steps:

- Identification – Collection of records from databases
- Screening – Removal of duplicates and irrelevant studies
- Eligibility – Full-text assessment of selected articles
- Inclusion – Final studies included for review analysis

Results and Discussion

Drug Profile of Ranitidine

Ranitidine was introduced as an effective therapeutic agent for the management of peptic ulcer disease and other acid-related gastrointestinal disorders. Pharmacologically, it acts by selectively inhibiting histamine H_2 receptors located on gastric parietal cells, thereby decreasing both basal and stimulated gastric acid secretion. Its reliable clinical performance, favourable tolerability, and affordability contributed to its widespread use as a first-line acid-suppressive medication for many years[1-3].

Table 4: Databases Used

Database/Source	Purpose
PubMed	Biomedical and clinical research articles
Scopus	Peer-reviewed scientific literature
ScienceDirect	Pharmaceutical and toxicological studies
Google Scholar	Additional relevant publications
FDA	Regulatory updates and safety communications
EMA	European regulatory assessment
WHO	Drug safety information

Table 5: Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Publication year	2018–2026	Before 2018 (except important historical data)
Language	English	Non-English articles
Study type	Research articles, reviews, regulatory reports	Editorials, unrelated reports
Topic	Ranitidine, NDMA, toxicity, cancer risk	Other unrelated impurities
Data availability	Full-text available studies	Incomplete information

Table 6: Drug Profile of Ranitidine

Parameter	Description
Generic name	Ranitidine
Drug class	Histamine H_2-receptor antagonist
Chemical category	Nitroethenediamine derivative
Molecular formula	$C_{13}H_{22}N_4O_3S$
Molecular weight	314.40 g/mol
Mechanism of action	Selective blockade of H_2 receptors on gastric parietal cells
Pharmacological action	Decreases gastric acid and pepsin secretion
Therapeutic uses	Peptic ulcer disease, GERD, Zollinger–Ellison syndrome
Routes of administration	Oral, intravenous, intramuscular
Bioavailability	Approximately 50%
Plasma half-life	About 2–3 hours
Metabolism	Mainly hepatic metabolism
Elimination	Primarily renal excretion
Major safety concern	Formation of NDMA impurity

ISSN 2583-2069

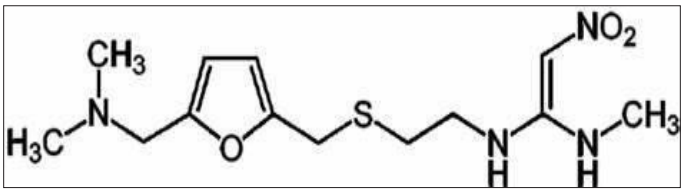

Figure 1.Chemical Structure of Ranitidine

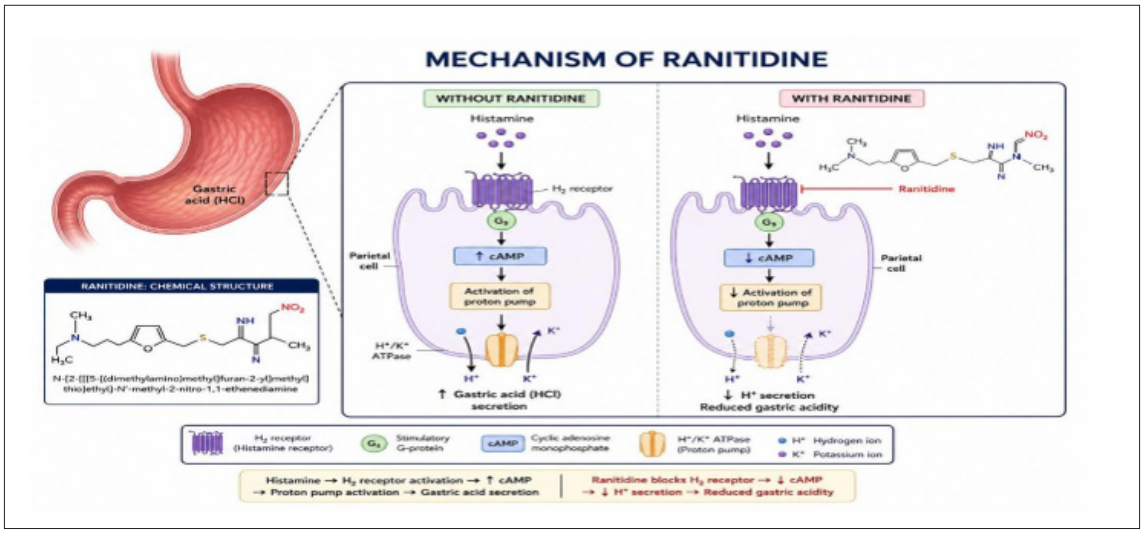

Figure 2.Mechanism of Ranitidine

Chemical Structure and Properties

Ranitidine belongs to the furan-containing Nitroethenediamine class of H_2 receptor antagonists. The molecule contains a furan ring, thioether linkage, and Nitroethenediamine group responsible for its pharmacological activity.

ChemicalFormula: $C_{13}H_{22}N_4O_3S$

Molecular Weight: 314.40 g/mol

Mechanism of Action: The pharmacological action of ranitidine is mediated through selective blockade of histamine H_2 receptors on gastric parietal cells. By preventing histamine-induced receptor activation, the drug suppresses the adenylate cyclase–cAMP signalling pathway, leading to reduced stimulation of the H^+/K^+-ATPase proton pump and a subsequent decline in gastric acid secretion.

Pharmacological Effects

- Suppresses basal (resting) gastric acid secretion.
- Lowers acid production during the night.
- Accelerates the healing of gastric and duodenal ulcers.
- Relieves symptoms associated with gastroesophageal reflux disease (GERD)
- Protects the gastric mucosa by minimizing acid-induced injury.

Therapeutic Applications

1. Peptic Ulcer Disease (PUD)

- Facilitates ulcer repair through effective suppression of gastric acid secretion.

2. Gastroesophageal Reflux Disease (GERD)

- Improves reflux-related symptoms by reducing acid exposure to the esophagus.

3. Zollinger–Ellison Syndrome

- Helps manage excessive gastric acid secretion caused by gastrin-producing tumors.

4. Functional Dyspepsia

- Provides relief from upper abdominal discomfort associated with acid-related indigestion.

5. Stress Ulcer Prophylaxis

Used to reduce the likelihood of stress-related gastric ulceration in critically ill patients.

NDMA Formation in Ranitidine

N-Nitrosodimethylamine (NDMA) is a nitrosamine compound classified as a probable human carcinogen (Group 2A) by the International Agency for Research on Cancer (IARC). NDMA contamination in ranitidine products became a major pharmaceutical safety concern after detection of elevated NDMA levels in 2019.

Ranitidine contains a dimethylamine moiety and a nitro group, which can contribute to NDMA formation under specific environmental conditions. The degradation of ranitidine may occur during storage, especially under conditions of increased temperature, humidity, and prolonged exposure.

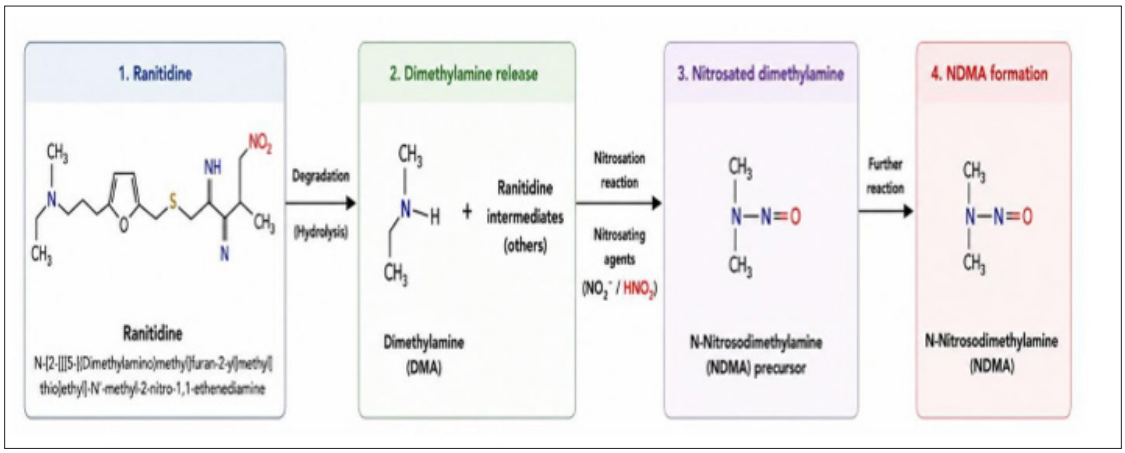

Figure 3.Mechanism of NDMA Formation

Table7: Major Studies on NDMA Formation in Ranitidine

Study/ Year	Major Findings
FDA Investigation (2019)	Detected NDMA impurity in ranitidine products and initiated safety evaluation
EMA Assessment (2020)	Confirmed presence of NDMA and recommended suspension of ranitidine medicines
Laboratory Stability Studies (2020-2022)	Demonstrated increased NDMA formation under elevated temperature conditions
Analytical Studies (2021-2025)	Developed sensitive LC-MS/MS methods for NDMA detection

Mechanism of NDMA Formation: NDMA formation from ranitidine occurs through chemical degradation and nitrosation reactions:

The dimethylamine group released from ranitidine can react with nitrosating agents such as nitrite under suitable conditions, resulting in the formation of NDMA.

Factors Affecting NDMA Formation

- Temperature
- Storage Duration
- Environmental Conditions
- Formulation Characteristics

Analytical Detection of NDMA: Various analytical techniques have been developed for NDMA estimation in pharmaceutical products:

- Gas Chromatography–Mass Spectrometry (GC-MS)
- Liquid Chromatography–Mass Spectrometry (LC-MS/MS)
- High-Performance Liquid Chromatography (HPLC) methods

Among these, LC-MS/MS is commonly preferred due to its high sensitivity, specificity, and ability to detect trace levels of nitrosamine impurities.

Pharmaceutical Significance: The discovery of NDMA contamination in ranitidine highlighted the importance of:

- Comprehensive impurity profiling
- Stability-indicating analytical methods
- Risk assessment of pharmaceutical impurities
- Continuous post-marketing surveillance

The ranitidine case became a significant example of the need for strict control of nitrosamine impurities in pharmaceutical manufacturing.

Toxicological Mechanism of NDMA

NDMA is a nitrosamine impurity classified as a probable human carcinogen (IARC Group 2A). After absorption, it is metabolized in the liver by cytochrome P450 2E1 (CYP2E1) into reactive metabolites.

These metabolites cause DNA alkylation, particularly the formation of O^6-methylguanine, leading to DNA damage and genetic mutations. NDMA also increases the production of reactive oxygen species (ROS), resulting in oxidative stress, inflammation, and cellular injury.

Prolonged exposure to NDMA may contribute to the development of liver, stomach, colorectal, kidney, and bladder cancers. Therefore, strict monitoring and control of NDMA impurities in pharmaceutical products are essential.

Cancer Risk Evidence

Several studies have investigated the association between ranitidine-associated NDMA exposure and cancer risk. Experimental studies indicate that NDMA is a genotoxic and probable human carcinogen, whereas epidemiological studies have shown mixed findings regarding the cancer risk in ranitidine users.

ISSN 2583-2069

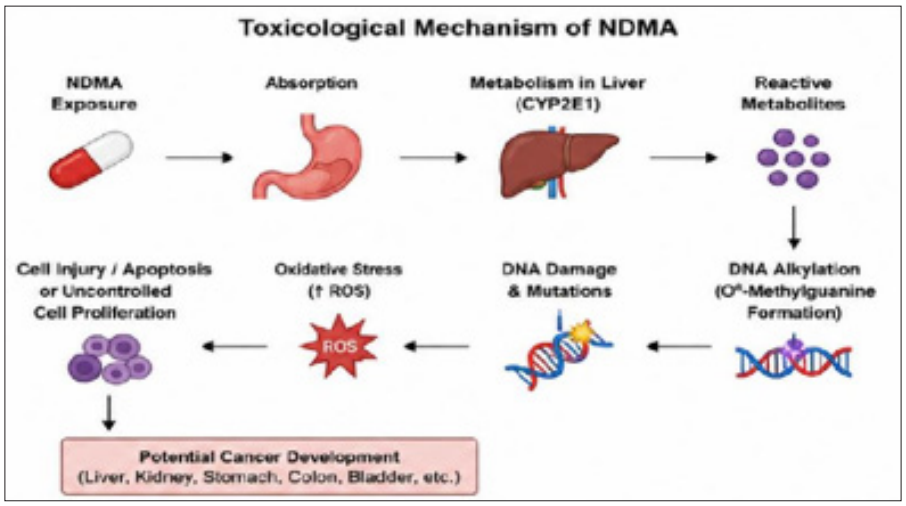

Figure 4.Toxicological Mechanism of NDMA

Table 8: Toxicological Effects of NDMA

Target Organ	Toxicological Effect	Possible Clinical Outcome
Liver	DNA damage, hepatotoxicity	Liver cancer
Stomach	Oxidative stress	Gastric cancer
Esophagus	Cellular mutation	Esophageal cancer
Colon	DNA alkylation	Colorectal cancer
Kidney	Oxidative injury	Renal dysfunction
Bladder	Genotoxicity	Bladder cancer

Some observational studies reported a possible association between long-term ranitidine use and cancers of the liver, stomach, bladder, and colorectum. However, other large population-based studies did not find a statistically significant increase in overall cancer incidence. Due to these inconsistent findings, a direct causal relationship between ranitidine use and cancer has not been conclusively established.

As a precautionary measure, regulatory agencies such as the FDA, EMA, and WHO recommended the withdrawal of ranitidine products because of unacceptable NDMA impurity levels rather than confirmed clinical evidence of increased cancer risk.

Regulatory Actions

After confirmation of NDMA contamination, regulatory authorities implemented several precautionary measures.

- U.S. Food and Drug Administration (FDA): Requested withdrawal of all ranitidine products from the U.S. market. Recommended patients discontinue OTC ranitidine. Advised manufacturers to investigate nitrosamine impurities.
- European Medicines Agency (EMA): Suspended marketing authorization for ranitidine-containing medicines. Required manufacturers to provide additional safety data.
- Central Drugs Standard Control Organization (CDSCO): Directed manufacturers in India to investigate NDMA contamination. Suspended or recalled affected products when necessary.

These regulatory actions significantly reduced public exposure to contaminated products.

Table 9: Summary of Cancer Risk Evidence

Study Type	Key Findings
Experimental studies	NDMA causes DNA damage and is carcinogenic in animals.
Observational studies	Some studies reported increased risk of certain cancers.
Population-based studies	No consistent increase in overall cancer risk.
Regulatory review	Withdrawal based on NDMA contamination and patient safety concerns.

Table 10: Epidemiological evidence evaluating cancer risk associated with ranitidine exposure

Study	Country/Data source	Design	Population	Comparator	Main findings	Interpretation
Yoon et al., 2021	South Korea	Cohort	50,610 matched users	Famotidine	No significant increase in overall cancer	No evidence of increased overall cancer
Adami et al., 2021	Denmark	Cohort	Large national cohort	H2RAs/PPIs	Mixed site-specific findings	Inconclusive
Iwagami et al., 2021	Japan	Cohort	Large claims database	Other H2RAs	No clear increase for major cancers	No consistent association
Joung et al., 2022	South Korea	Cohort	25,360 after matching	Other H2RAs	HR 0.98 (95% CI 0.81–1.20)	No significant association
Lai et al., 2023	Multinational	Cohort	1,183,999	Other H2RAs	HR 1.04 (95% CI 0.97–1.12)	No significant increase

Table 11: Future Research Priorities

Research Area	Future Direction
Drug formulation	Develop NDMA-free and more stable formulations
Analytical methods	Improve sensitive detection techniques (LC-MS/MS, GC-MS)
Toxicology	Conduct long-term safety and carcinogenicity studies
Regulatory science	Strengthen global nitrosamine guidelines
Pharmacovigilance	Enhance post-marketing safety monitoring

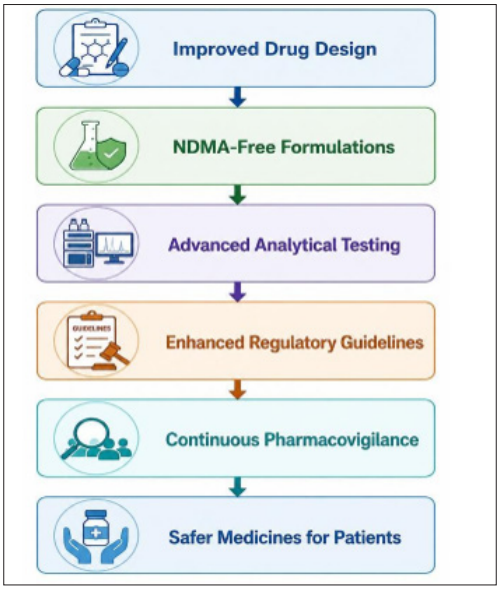

Figure 5.Future Perspective

Alternative Medications

Following ranitidine withdrawal, healthcare professionals recommended safer alternatives including:

- Famotidine (H_2-receptor antagonist)
- Omeprazole (Proton Pump Inhibitor)
- Pantoprazole
- Esomeprazole
- Rabeprazole

These medicines have not shown the same NDMA contamination concerns under normal manufacturing conditions.

Future Perspectives

Although ranitidine has been withdrawn from many markets, the issue of NDMA contamination has emphasized the need for improved pharmaceutical quality control. Future research should focus on developing more stable formulations, identifying safer alternatives, and implementing advanced analytical techniques for the early detection of nitrosamine impurities.

ISSN 2583-2069

Further long-term epidemiological studies are required to better understand the association between NDMA exposure and cancer risk in humans. In addition, regulatory agencies should continue strengthening guidelines for impurity control, stability testing, and post-marketing surveillance to ensure the safety and quality of pharmaceutical products

Conclusion

Ranitidine was widely used as an effective H_2-receptor antagonist for the treatment of acid-related disorders. However, the discovery of N-nitrosodimethylamine (NDMA) contamination raised significant concerns regarding its long-term safety and led to the global withdrawal of ranitidine products.

This review highlights the pharmacology of ranitidine, the mechanism of NDMA formation, its toxicological effects, available cancer risk evidence, and the regulatory actions taken worldwide. Although current human evidence linking ranitidine directly to cancer remains inconclusive, the carcinogenic potential of NDMA has emphasized the need for strict impurity control and continuous safety monitoring.

Future efforts should focus on developing safer pharmaceutical formulations, improving analytical detection methods, and strengthening regulatory guidelines to ensure the quality, efficacy, and safety of medicines.

Conflict of Interest

The authors do not have any conflicts of interest.

References

1. U.S. Food and Drug Administration. Laboratory tests: Ranitidine. Silver Spring (MD): FDA; 2020.
2. U.S. Food and Drug Administration. FDA approves reformulated ranitidine following comprehensive safety review. 2025.
3. European Medicines Agency. EMA to review ranitidine medicines following detection of NDMA. Amsterdam: EMA; 2019.
4. European Medicines Agency. Ranitidine-containing medicinal products – referral. Amsterdam: EMA; 2020.
5. European Medicines Agency. Suspension of ranitidine medicines in the EU. Amsterdam: EMA; 2020.
6. International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: N-Nitrosodimethylamine (NDMA). Lyon: IARC.
7. World Health Organization. WHO pharmaceuticals newsletter: Nitrosamine impurities in medicines. Geneva: WHO 2019.
8. Schlingemann J, et al. Nitrosamine impurities in medicines: Sources, analytical methods and regulatory perspectives. J Pharm Biomed Anal. 2021.
9. Gao X, et al. Analytical determination of N-nitrosodimethylamine in pharmaceutical products: A review. TrAC Trends Anal Chem. 2021.
10. Li Y, et al. Formation mechanism and analytical detection of nitrosamine impurities in pharmaceuticals. J Pharm Sci.2022;111(10):2651.
11. Avula B, et al. Determination of NDMA in ranitidine drug products by LC–MS/MS. J Pharm Biomed Anal. 2020.
12. Parr MK, et al. Nitrosamine impurities in medicines: Current status and future perspectives. Drug Saf. 2021.
13. US Pharmacopeia. Nitrosamine impurities in pharmaceuticals. USP; 2021.
14. European Directorate for the Quality of Medicines & HealthCare (EDQM). Guidance on nitrosamine impurities. Strasbourg: EDQM;2020.
15. International Council for Harmonization (ICH). ICH Q3A(R2): Impurities in New Drug Substances2006.
16. International Council for Harmonization (ICH). ICH Q3B(R2): Impurities in New Drug Products2006.
17. International Council for Harmonization (ICH). ICH M7(R2): Assessment and Control of DNA Reactive (Mutagenic) Impurities2023.
18. Valisure LLC. Citizen Petition on NDMA in Ranitidine Products. 2019.
19. Health Canada. Ranitidine and NDMA safety review. Ottawa: Health Canada.
20. Central Drugs Standard Control Organization (CDSCO). Safety advisory regarding ranitidine and NDMA. New Delhi: CDSCO.