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A Review on Ranitidine with NDMA Contamination

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ABSTRACT

N-nitrosodimethylamine (NDMA) is a semi-volatile chemical molecule that the International Agency for Research on Cancer has classified as possibly carcinogenic. It can originate from industrial or natural processes related to the N-nitrosamine family and is present in several medicinal medicines, such as angiotensin II receptor blockers and ranitidine. Ranitidine's NDMA contamination resulted in regulatory measures and the drug's removal from distribution. Sensitive analytical methods such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) or gas chromatography-mass spectrometry (GC-MS) are needed to analyze NDMA levels. Humans can safely consume up to 0.96ng, or 0.32 ppm, of NDMA daily. Numerous processes, including temperature, acidity, light exposure, metal ions, and manufacturing procedures, are involved in synthesis of NDMA from ranitidine. Adverse health effects, including cancer, kidney illness, and liver damage, have been associated with NDMA exposure. Regular testing, the use of substitute ingredients, adherence to good manufacturing procedures, cooperation, and ongoing risk assessment are examples of preventive methods to prevent contamination. Since research is currently being done to discover alternative drugs and treatment techniques for illnesses related to acid reflux, the future of ranitidine is yet uncertain. The function of ranitidine in clinical practice has changed as a result of recalls and safety concerns, and its position will continue to be influenced by ongoing research and regulatory changes. In conclusion, the discovery of NDMA contamination in ranitidine has prompted serious health concerns, regulatory actions, and the investigation of substitute drugs and safety precautions.

INTRODUCTION:

NDMA is a semi-volatile, organic compound that is formed by either natural or industrial processes from the N-nitrosamine family with carcinogenicity [1]. NDMA has the chemical formula C2H6N2O (Fig. 1). Its structure consists of a dimethylamine group bonded to a nitroso group (N–N=O) [2]. NDMA is also recognized as a probable carcinogen by the International Agency for Research on Cancer [3]. NDMA contamination has been reported in various pharmaceutical products, including angiotensin II receptor blockers (ARBs) and ranitidine (Zantac), a popular medication for heartburn and acid reflux [4]. Analyzing NDMA levels requires sensitive analytical techniques such as gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS). These methods allow for accurate quantification of NDMA in various matrices [5]. Various tests from the FDA showcase an increase in NDMA levels with storage time [6]. Also, the safe dose of NDMA in humans per day is ≤ 0.96ng on ingestion or 0.32 ppm per day [7]. Earlier, NDMA was used as an additive for lubricants and as an antioxidant to produce liquid fuel [8].

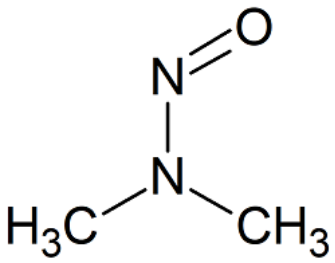


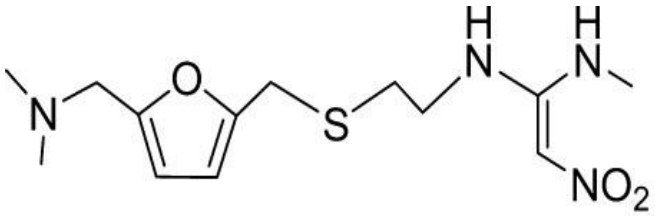
Fig. 1: Chemical structure of NDMA

Sources of NDMA:

NDMA is found in water, foods (like dairy products and vegetables), and several industrial processes (Quenching Process) [9-11]. In foods, the nitrosating agent responsible for forming NDMA is usually nitrous anhydride, which arises from nitrite in an acidic aqueous solution, as in the stomach [12]. Inhaling tobacco smoke, or using rubber items and cosmetics often results in exogenous exposure to nitrosamines [13]. NDMA can be found in certain foods and beverages, particularly those processed with sodium nitrite, such as cured meats and fish. It is also detected in alcoholic beverages like beer and whiskey [14].

Ranitidine and its history:

Ranitidine is an API in the ranitidine pharmaceutical preparations, generally taken as OTC (Over the Counter) medicine which helps to get relief from heartburn and gastric ulcers [15]. Ranitidine was discovered by scientists at Glaxo (now GlaxoSmithKline) in the late 1970s as part of efforts to develop a more potent and longer-lasting alternative to cimetidine, the first H2 receptor antagonist [16]. The chemical structure of ranitidine includes functional groups of nitro, secondary and tertiary amines (Fig. 2). Ranitidine was first approved for medical use in 1981 and quickly became one of the most widely prescribed medications globally due to its effectiveness and relatively low incidence of side effects [17]. Ranitidine works by blocking histamine H2 receptors in the stomach, thereby reducing the production of gastric acid by parietal cells, leading to decreased acidity in the stomach [18]. Ranitidine is primarily prescribed to treat gastrointestinal conditions such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome, among others [19]. Ranitidine has been marketed under various brand names, including Zantac, Histac, Ranitic, and Zantac 360, among others, depending on the country and manufacturer [20].



Ranitidine

Fig. 2 Chemical structure of Ranitidine molecule.

Contamination of NDMA in Ranitidine:

Ranitidine was generally considered safe for many years, with rare reports of adverse effects such as headaches, dizziness, and gastrointestinal disturbances. It was well-tolerated by most patients [21]. The U.S. Food and Drug Administration (FDA) conducted investigations into the presence of NDMA in ranitidine products and issued warnings to healthcare professionals and consumers regarding the potential risks. In September 2019, the FDA found out that one of the ranitidine preparations (Zantac®) had unacceptable levels of NDMA [6]. In the last 12 years, there have been more than 20 studies that have proved ranitidine as a precursor of NDMA [22-26]. In one of the studies, ranitidine showed a greater potential in the formation of NDMA [25]. In a laboratory study using liquid chromatography-high-resolution mass

spectrometry presented that under simulated gastric conditions, a vital source of NDMA could be ranitidine [27]. A major action taken after this is that ranitidine is discontinued from market [6]. Regulatory agencies in various countries, including the European Medicines Agency (EMA) and Health Canada, also conducted investigations and took regulatory actions, including recalls and suspensions of ranitidine products [28]. Following the recalls and concerns over NDMA contamination, numerous lawsuits were filed against manufacturers of ranitidine products, alleging failure to warn consumers about the potential risks [8]. Ranitidine was available in both brand-name and generic formulations, making it accessible to a wide range of patients. However, generic versions were also affected by the recalls and regulatory actions [29].

Formation of NDMA:

In the presence of either mono or dichloramine precursors, ranitidine was found to form NDMA. Under numerous amine precursors, it suggests the higher potential of ranitidine to synthesize NDMA [26]. Reports suggests that on the spontaneous breakdown of the ranitidine molecule, there is a formation of dimethylamine and nitrites which could lead to the formation of NDMA [30-31]. Another contributing factor in the NDMA formation process is claimed to be the packaging material (i.e. nitrocellulose) [32]. It has been suggested that chloramination of ranitidine is the formulation mechanism of NDMA. The formation of NDMA is mainly determined by chloramine and precursor amine groups, both of which are highly dependent on pH [33]. NDMA can be formed during various industrial processes, including the production of rocket fuel, lubricants, and certain chemical reactions. It is also detected in water bodies due to wastewater discharge and agricultural runoff [34].

Conditions for NDMA formation:

NDMA formation from ranitidine can increase at high temperatures, especially during storage or transportation. Elevated temperatures can facilitate the degradation of ranitidine and subsequent NDMA formation [35]. There is a 20% degradation of ranitidine caused by to temperature of 45°C and absolute humidity of 45% [36]. Ranitidine samples failed the test of stability and were found unstable at 40 and 55°C temperatures [37]. NDMA formation from ranitidine can occur over time, especially during storage or when the drug is past its expiration date [6]. It could take just 5 days for the formation of NDMA from ranitidine at measurable levels [22]. Acidic conditions can promote the conversion of ranitidine into NDMA. In acidic environments, ranitidine may undergo chemical transformations that

increase the likelihood of NDMA formation [38]. Exposure to light, especially ultraviolet (UV) radiation, can accelerate the degradation of ranitidine and promote NDMA formation. Light-induced reactions may facilitate the conversion of ranitidine into NDMA and other potentially harmful compounds [39]. Certain metal ions, such as copper and iron, can catalyse reactions that lead to NDMA formation from ranitidine. Contamination with metal ions, either from the environment or packaging materials, may increase the risk of NDMA contamination [40]. Variations in manufacturing processes, including synthesis, purification, and formulation, can influence the potential for NDMA formation in ranitidine-containing products. Differences in production methods may result in varying levels of impurities or degradation products that contribute to NDMA formation [41].

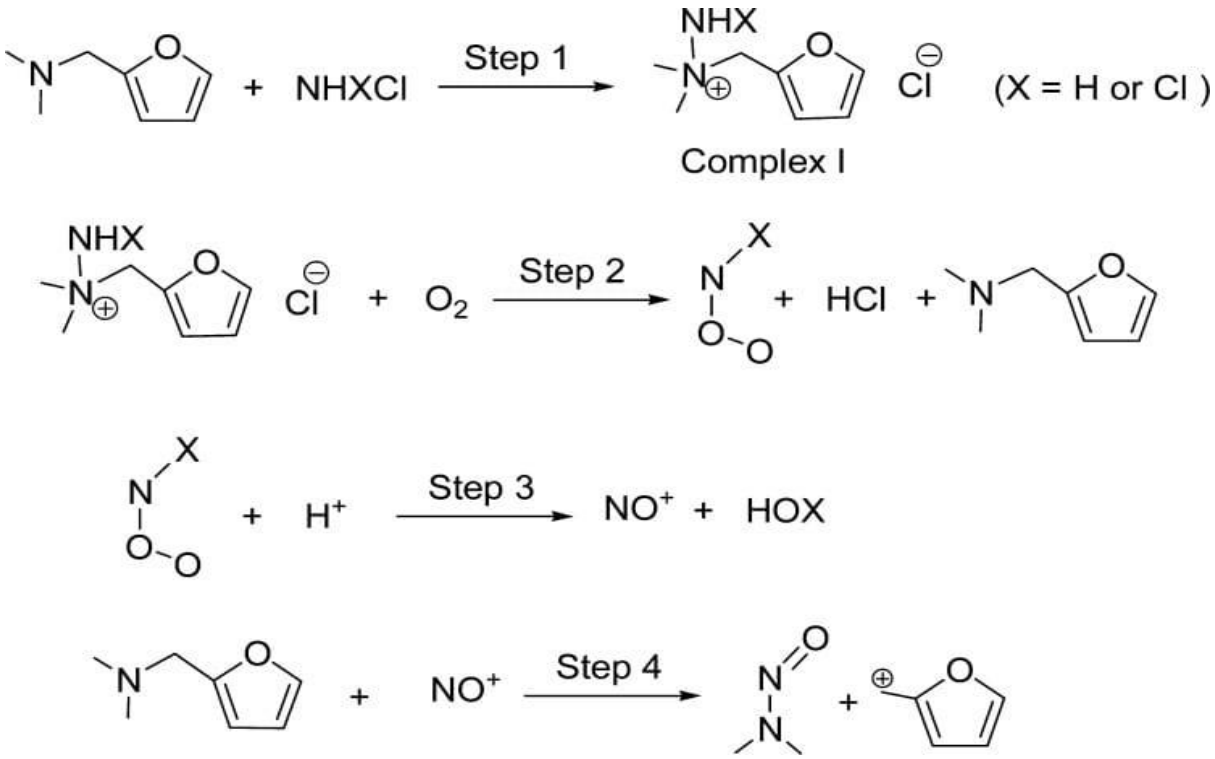
Mechanism:

Step 1: The initial step involves the nitrosation of the tertiary amine. This reaction typically occurs under acidic conditions in the presence of nitrous acid (HNO2). Nitrous acid can be generated in situ from sodium nitrite (NaNO2) and an acid such as hydrochloric acid (HCl). In this step, the amine reacts with nitrous acid to form a nitrosamine intermediate.

Step 2: The nitrosamine intermediate undergoes a proton transfer reaction. This step involves the transfer of a proton from an acidic species, such as water or the solvent, to the nitrogen atom of the nitrosamine. This proton transfer results in the formation of a nitrosonium ion.

Step 3: The nitrosonium ion undergoes a rearrangement reaction, leading to the formation of a diazonium salt. This rearrangement typically involves the migration of a proton and the formation of a nitrogen-nitrogen double bond.

Step 4: Finally, the diazonium salt reacts with another molecule of the tertiary amine through a nucleophilic substitution reaction. This reaction results in the formation of N-nitrosodimethylamine (NDMA) and a secondary amine as a byproduct.



Diseases due to NDMA contamination in Ranitidine:

NDMA, found in the ranitidine preparations, was discovered to produce cancer in several experimental species of animals and also caused hyperplastic nodules and cirrhosis in monkeys [42-44]. Exposure to NDMA has been linked to various adverse health effects, including liver damage, kidney disease, and cancer. Acute exposure to high levels of NDMA can result in immediate toxicity, while chronic exposure may lead to long-term health problems [6]. The use of ranitidine leads to a significant increase in the risk of breast, testicular, thyroid, and kidney cancer [45]. On studying the propensity score-matched cohort between ranitidine and other H2RAs, it was found that the risk of kidney cancer related to ranitidine use was observed to be greater than other H2RAs use [46].

Precautions to avoid NDMA contamination:

- Regular Testing and Monitoring: Implementing rigorous testing protocols to detect NDMA contamination at various stages of manufacturing can help prevent its presence in ranitidine formulations. This includes testing raw materials, intermediates, and finished products [7].

- Use of Alternative Ingredients: Exploring alternative ingredients or formulations that do not produce NDMA during the manufacturing process can be an effective preventive

measure. This might involve replacing specific components prone to NDMA formation with safer alternatives [47].

- Adopting Good Manufacturing Practices (GMP): Strict adherence to GMP guidelines can minimize the risk of NDMA contamination by ensuring proper manufacturing processes, equipment maintenance, and cleanliness standards are met [48].

- Collaboration and Information Sharing: Collaborating with regulatory agencies, industry partners, and research institutions to share information and best practices regarding NDMA contamination prevention can help identify emerging risks and develop effective strategies to mitigate them [49].

- Continuous Risk Assessment and Improvement: Implementing a robust risk assessment framework to continually evaluate the potential sources and risks of NDMA contamination in ranitidine products. This includes regularly reviewing manufacturing processes, conducting root cause analysis, and implementing corrective and preventive actions as needed [42].

Present and Fortune of Ranitidine:

Ongoing research is focused on developing novel approaches for NDMA detection, removal, and risk assessment. This includes the exploration of alternative disinfection methods, adsorption materials, and predictive modeling techniques [50]. In light of the recalls and safety concerns, patients and healthcare providers have turned to alternative medications such as proton pump inhibitors (PPIs) and lifestyle modifications for the management of acid-related disorders [51]. The pharmaceutical industry and academic researchers continue to explore and develop alternative medications and treatment strategies for acid-related disorders, focusing on efficacy, safety, and long-term outcomes [52]. While ranitidine remains an important drug in the treatment of certain conditions, its future has been significantly impacted by recalls and regulatory actions. Ongoing research and regulatory developments will shape its role in clinical practice [53].

Conclusion:

Because of its carcinogenic qualities and frequent occurrence in several pharmaceutical drugs, most notably ranitidine (Zantac) and angiotensin II receptor blockers, N-nitrosodimethylamine (NDMA) is a substance that should be taken very seriously. It can arise as a result of industrial or natural activities involving the N-nitrosamine family. When it was

discovered that ranitidine, a common medicine for acid reflux and heartburn, contained excessive amounts of NDMA, it was taken off the market, and regulatory actions were taken.

Because of the significant health hazards associated with NDMA contamination, which include cancer, kidney illness, and liver damage, preventative measures like routine testing, the use of substitute chemicals, adherence to good manufacturing procedures, teamwork, and ongoing risk assessment are necessary. The process by which ranitidine is converted into NDMA comprises multiple processes that are impacted by several variables, including temperature, acidity, exposure to light, and metal ions.

The development of alternative drugs and preventative measures is the main focus of continuing research, but ranitidine's future is yet unknown. In light of recalls and safety concerns, patients and healthcare providers have resorted to other medications, such as proton pump inhibitors. Researchers and the pharmaceutical sector are still looking for new methods for NDMA elimination, detection, and risk assessment.

To maintain public safety and create effective solutions for controlling illnesses associated with acidity, regulatory agencies, industry stakeholders, and researchers must work together to address NDMA contamination. The future landscape of NDMA-related problems and the usage of drugs like ranitidine in clinical practice will be greatly influenced by ongoing research and regulatory advancements.

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