What is N-nitrosodimethylamine and Why is it Dangerous?

N-nitrosodimethylamine (NDMA) is a chemical shown to induce tumor formation in the gastrointestinal tract, liver, lungs, and kidneys in animals. NDMA directly activates RAS oncogenes, and methylidazinium, its methylated metabolite, is also a mutagen. International organizations ranging from the Environmental Protection Agency to the World Health Organization (WHO) International Agency for Research on Cancer have classified NDMA as a probable carcinogen.

The US Food and Drug Administration (FDA) has set an acceptable level of NDMA in each finished drug product (tablet or capsule) at no more than 96 ng (0.096 μg). Although this is less than the 190 ng of daily exposure to NDMA that the WHO finds acceptable, this is in addition to NDMA ingested from food, tap water, and other NDMA-containing drugs and dietary supplements.

To date, the FDA has found excessive amounts of NDMA in several lots of angiotensin receptor blockers (ie, valsartan, losartan, and irbesartan), metformin extended release products, and ranitidine tablet and syrup products.

Where Does Ranitidine's NDMA Come From?

Angiotensin receptor blockers and metformin extended release products are contaminated with NDMA during the problematic manufacture of the active pharmaceutical ingredient or the finished pharmaceutical product. This means that finding an acceptable amount of NDMA in the active pharmaceutical ingredients or finished drug products at the time of manufacture assures that regardless of the time that passes, additional NDMA will likely not be found. Unfortunately, ranitidine can be contaminated with NDMA during the manufacturing process, but as the ranitidine molecule degrades, new NDMA can be created as well.

A study by Emery Pharma assessed the creation of NDMA during the natural degradation of the ranitidine active pharmaceutical ingredient and finished drug product over time at different temperatures. The study found that 150 mg of ranitidine tablets USP contained 18 ng of NDMA at baseline, but after storing it at 25 °C for 12 days, NDMA dosages increased to 25 ng, and storing it at 70 °C resulted in a dose increased to 142 ng. Ranitidine 150 mg, sold as Zantac Cool Mint, was found to increase from 19 ng NDMA at baseline to 70 ng NDMA when stored at 70 °C for 14 days, just below of the FDA's maximum acceptable level. This means that having an acceptable amount of NDMA at the time of manufacture does not assure this will be the case on the day an individual ingests it. Shortening the expiration date and strictly controlling ranitidine's storage conditions throughout the supply chain and in patients' homes would be needed to mitigate the risk. This would be a difficult but surmountable obstacle.

The study by Braunstein et al explores whether it is possible to create NDMA in the stomach after ingestion using an in vitro model. In a simulated stomach acid pH of 2.5, there was a relationship between the generation of NDMA as the concentration of sodium nitrite increased from 1 mmol/L to 100 mmol/L. This suggests that when nitrogenous products are in the stomach at the same time as ranitidine, there would be an accelerated generation of NDMA. Similarly, with a fixed amount of sodium nitrate (50 mmol/L), the researchers found a relationship between reducing the pH from 5.5 to 2.5 and the amount of NDMA created. The NDMA dosages created with standard doses of ranitidine were more than 10 000 ng, an alarming amount.
The study by Braunstein et al.\(^4\) was an in vitro study with a simulated gastric environment, not a real stomach churning with real stomach contents. However, the results are bolstered by a 2016 clinical study by Zeng and Mitch,\(^5\) in which urine samples were collected from 5 women and 5 men over 24 hours before and after consumption of ranitidine 150 mg tablets. After ranitidine intake, the urinary NDMA increased from a baseline of 110 ng/d to 47 600 ng/d. Unfortunately, Zeng and Mitch did not test the ranitidine tablets for NDMA before use, so whether the NDMA was created in the tablets or in the human body could not be ascertained.

The FDA has developed their own simulated gastric fluid model to assess the generation of NDMA. The FDA has stated that no additional NDMA generation occurred in their ranitidine stomach model, but they have not divulged their actual results.\(^1\) It is possible that the FDA’s methods have nuanced differences compared with the study by Braunstein et al.,\(^4\) but it is impossible to know for certain with the information currently available.

There are some preliminary data suggesting that the use of ranitidine is associated with developing cancer. In a rodent study by Brambilla et al.,\(^6\) it was shown that the addition of ranitidine and sodium nitrite increased the percentage of DNA fragmentation and formation of sister chromatids exchanges or diploid cells. In addition, a preliminary observational study by Mathes et al.\(^7\) assessed the association between use of H2 blockers and risk of different types of breast cancer. Current users of ranitidine were found to have a significantly increased risk of ductal carcinoma but neither cimetidine nor famotidine were associated with increased risk. While these studies are far from conclusive, there are safer alternatives.

**Where Do We Go from Here?**

Researchers need to prospectively assess other drugs with dimethylamine groups to determine if they can create NDMA if stored at higher temperatures and to determine whether NDMA can be created after ingestion as well. A list of candidate drugs with dimethylamine groups bound to an electron-rich moiety has been identified in a water chlorination study.\(^8\) Investigators added 25 nmol/L concentrations of 8 dimethylamine group-containing drugs and ranked the amount of NDMA created when they added 28.4 mg/L chloramine (commonly used water disinfectant) at a pH of 7.0 and temperature of 21 °C. They found that 94% of ranitidine was converted to NDMA at 24 hours. This is much higher than that found for 2 H1-blocking antihistamines (doxylamine and chlorpheniramine), sumatriptan, nizatidine, diltiazem, and tetracycline, but all the drugs generated NDMA.\(^8\) If more than 10 000 ng of NDMA can be created by standard ranitidine doses, it is possible that some of these other finished pharmaceutical products could generate doses in excess of 96 ng. If NDMA is found in dangerous amounts after hot temperature storage or after ingestion, these drugs should likewise be avoided in lieu of other similarly effective alternatives.

**ARTICLE INFORMATION**


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**Conflict of Interest Disclosures:** None reported.

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