Risk navigator

Nitrosamine overview

Primary casualty

Table of contents

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Risk Solution Services provides technical insight related to existing and potential insured risk at Markel. The team partners with our customers, claims, and underwriters to educate on both current and future risk trends and supports our clients with a broad offering of risk management solutions.

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Table of contents

What are nitrosamines?

Nitrosamines are molecules containing the nitroso functional group. Several nitrosamines including NDEA, NDIPA, NEIPA, NMBA, and NDMA have been detected in medicines. This is of concern since they are all potential carcinogens. NDMA can be used to illustrate the general characteristics of nitrosamines. NDMA is shorthand for N-nitrosodimethylamine. Currently, NDMA is made only for research purposes but was formerly used in rocket fuel, antioxidants, lubricants, and softeners for copolymers. NDMA may be unintentionally produced via chemical reactions that occur in plants that manufacture amines, pesticides, rubber, tires, dyes, and surfactants. It is also present in tanneries. Work-related airborne exposures are possible. NDMA occurs as a byproduct in water purification and food preservation. A simple way to conceive of the process is that to get NDMA, the following overly simplified reaction occurs: N (nitrogen) + DMA =NDMA. Remember that nitrogen is the most plentiful element in the earth's atmosphere. There are plenty of chemical opportunities for N and DMA to get together.

Ingesting nitrite-preserved foods, such as, cured meats, salami, frankfurters, fish (smoked, dried, salted), and malt beverages (beer and whiskey) causes NDMA to be formed in the stomach. Breathing or inhaling cigarette smoke may cause NDMA exposure. Some shampoos and cleansers may contain NDMA. It is also found in drinking water. The primary source of human exposure is the oral route due to the consumption of contaminated food, water, or pharmaceuticals. It is estimated that infants consume 70 nanograms (ng) of NDMA per day, children 100 ng per day, adults 110 ng per day. (An explanation of nanograms and micrograms is included as an appendix.)

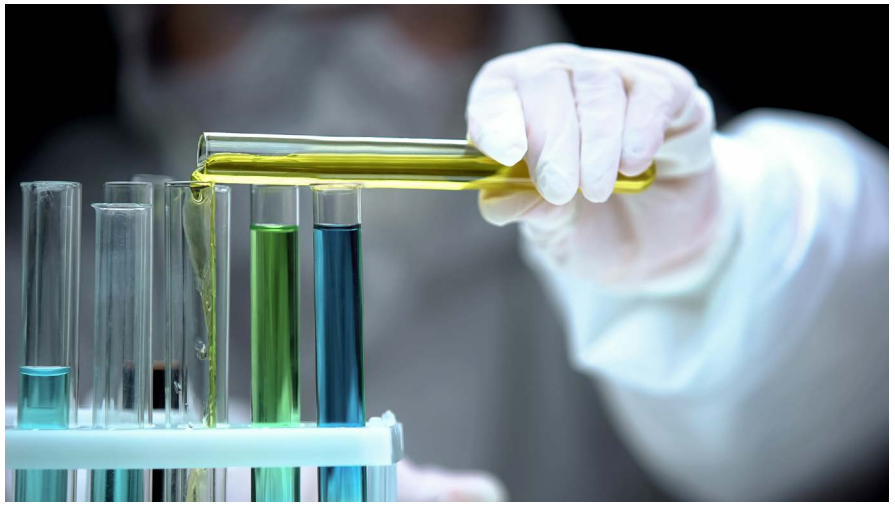

Table of contents

How is NDMA harmful?

NDMA has a direct toxic effect on the liver. An animal model demonstrated the destruction of several types of liver tissue. People poisoned with several hundred milligrams of NDMA experienced vomiting, diarrhea, and liver damage which could lead to death. NDMA has been classified as a probable human carcinogen based on animal studies. NDMA activates the cancer causing ras oncogene. When NDMA gets metabolized it forms methyldiazonium, which is known to cause mutations. In animal models, tumors occurred in the liver, respiratory tract, kidneys, and blood vessels. Therefore, NDMA has both localized and systemic cancer-causing effects. Although a direct link between NDMA and human cancers has not been firmly established, it is "reasonably anticipated to be a human carcinogen."

Environmental NDMA exposures

The EPA has established NDMA screening levels for tap water, soil, and air. Fifteen states have established drinking water and groundwater guidelines. They range from 0.00069 micrograms per liter in Colorado to 0.01 micrograms per liter in Massachusetts. The average for the group is 0.0041 micrograms per liter. It is prudent to minimize the intake of the nitrite-preserved foods described above. Obviously any NDMA ingested in medications will be an exposure in addition to that from food and water.

Table of contents

Medication NMDA exposures

The FDA works with manufacturers to remove products with nitrosamine impurity levels that are above interim acceptable limits. It also makes recommendations regarding how products should be tested. The FDA assesses particular batches and lots of medications. The testing focuses on analyzing active pharmaceutical ingredients (API) and the highest dosage strength available in the US market. When the FDA has completed a comprehensive assessment and found no nitrosamine impurities, the "not present" indication is given. When the assessment has not been completed the "TBD" (to be determined) label is applied. Testing results and interim exposure limits are subject to change and should be monitored closely. The FDA has set an **interim** exposure limit of 96 nanograms per day in a medication tablet or capsule. Senior citizens, those 65 and older, take a median number of four medications daily, which creates a multiplicative exposure of potentially 384 ng/day.

Table of contents

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NDMA is present in medications as a contaminant. Materials used in the manufacturing process may be contaminated with NDMA. There is some thought that packaging materials may also be tainted with NDMA. Chemical reactions in the manufacturing process may create NDMA. For example, one of the drugs under scrutiny, Valsartan, has a tetrazole ring, an aromatic five membered ring with one carbon atom and four nitrogen atoms. An American manufacturer used tributylin azide to form the tetrazole ring with xylene as a solvent. A Chinese manufacturer used sodium azide instead of tributylin and switched from xylene to dimethylformamide. This allowed for the formation of DMA. When sodium nitrite was added to get rid of the sodium azide, the combination of N + DMA = NDMA was achieved. Medications are combinations of active pharmacologic ingredients (APIs). Drug manufacturers should test each API as well as the end-product for contaminants.

As of September 23, 2019, the FDA reported that 1,159 lots of Valsartan, Losartan and Irbesartan were recalled because of NDMA contamination. These drugs are called angiotensin receptor blockers (ARBs) and are used to treat hypertension. An assessment of 17 Valsartan products for NDMA by the FDA found that 9 were fine, 3 had NDMA doses ranging from 330 to 620 ng/tablet, and five had NDMA doses ranging from 6,940 to 20,190 ng/tablet. Remember the standard of 96 ng.

Ranitidine (Zantac) is used to prevent ulcers in the stomach and intestines, and treat gastro-esophageal reflux and a syndrome in which the stomach produces too much acid. An online pharmacy, Valisure, tested ranitidine and found NMDA doses ranging from 23,600 to 304,500 ng/tablet. The FDA took issue with the process Valisure used. They thought the high temperature (266° F) created inaccurate values. Subsequent FDA testing revealed ranges from 0 to 860 ng/tablet. The possibility that ranitidine may be converted to NMDA if heated during storage, transport, or sun exposure after mail delivery. Ranitidine products were recalled on April 1, 2020.

Metformin, a drug used to treat high blood sugar, was recalled on June 1, 2020 due to unacceptable levels of NDMA. Metformin has both extended release (ER) and immediate release (IR) formulations. Valisure submitted 38 lots of Metformin to the FDA for testing. The amount of NDMA in 8 lots of the Metformin ER induced the FDA to request that five companies recall the product in June 2020.

Table of contents

Summary

- NDMA is ubiquitous with environmental exposures from air, water, and soil.
- Dietary NDMA (and other nitrosamines) are sources of exposure.
- A study of 5,150 patients evaluated of 4.6 years compared cancer risk of those who took NDMA contaminated Valsartan to those who took uncontaminated Valsartan revealed no increased incidence of cancer in the "contaminated" group.
- Longitudinal studies are needed to assess long term risk.
- Manufacturers should **comply with FDA testing guidelines and monitor changes in interim exposure limits.**
- Practitioners must be aware of contamination issues and consider alternate therapies.
- There are currently hundreds of individual lawsuits and at least one class action lawsuit against manufacturers and dispensers of drugs allegedly containing excessive amounts of NDMA.

Appendix

A kilogram is 1,000 grams and equals 2.2 pounds. So, 1 gram equals 0.0022 pounds. A microgram is a millionth (1 X 10-6) of a gram. A nanogram is a billionth (1 X 10-9) of a gram.

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Table of contents