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Nitrosamine Impurities: Sources and Control

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Introduction

In June 2018, FDA was informed of the presence of an impurity identified as N-nitrosodimethylamine (NDMA) in the angiotensin II receptor blockers (ARB) valsartan. Through investigation, the Agency determined that numerous lots of valsartan and a few other ARB drug products from different manufacturers contained unacceptable levels of nitrosamines. The drug product manufacturers voluntarily recalled the affected batches of these drug products.

In September 2019, FDA learned that some common heartburn products (ranitidine, commonly known as Zantac, and nizatidine, commonly known as Axid) contained unacceptable levels of NDMA. FDA recommended that manufacturers voluntarily recall ranitidine and nizatidine products with NDMA levels above what the Agency considers acceptable. FDA's testing suggests that NDMA levels increase with storage time. On April 1, 2020, FDA requested that all ranitidine products be withdrawn from the U.S. market.

In May 2020, FDA testing revealed that certain lots of metformin extended-release formulation contained NDMA above the Agency's recommended acceptable intake limit. Based on that testing, FDA requested that identified applicants voluntarily recall these lots of the extended-release metformin.

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FDA and other regulatory authorities have partnered to share information and to develop guidelines to mitigate the risk of nitrosamine impurities in drug products.

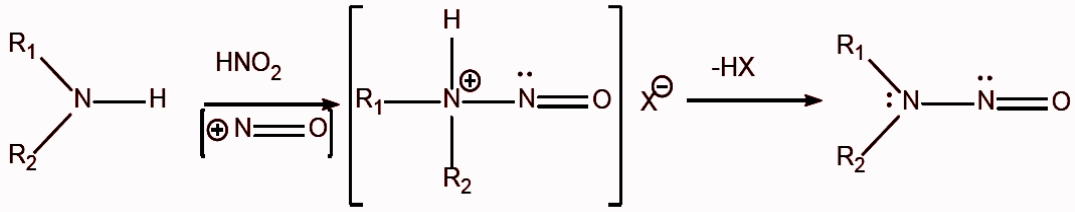
In this article, sources of nitrosamine and mitigation measures are discussed based on regulatory guidelines[1,2].

Keywords: Nitrosamine, NDMA, NDEA, FDA, EMA, ICH

What are Nitrosamine Impurities

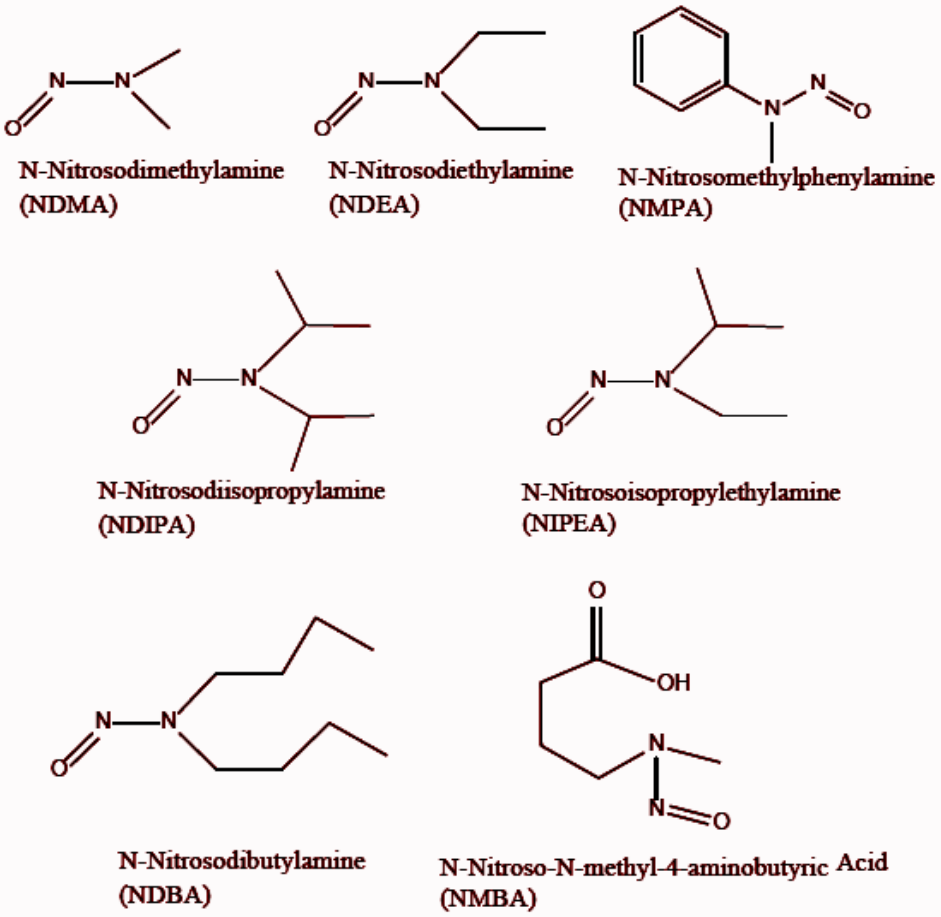
The term nitrosamine describes a class of compounds having the chemical structure of a nitroso group bonded to an amine ($R^1N(-R^2)-N=O$), as shown in Figure 1. The compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions).

Figure 1. Representative Reaction to Form Nitrosamines



FDA has identified seven nitrosamine impurities that theoretically could be present in drug products: N-Nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitrosoisopropylethyl amine (NIPEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), and N-nitrosomethylphenylamine (NMPA) (Figure 2). Five of them (NDMA, NDEA, NMBA, NIPEA, and NMPA) have actually been detected in drug substances or drug products.

Figure 2. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products



Sources of Nitrosamine Impurities

Following are the possible sources of nitrosamine impurities[1,2]:

1. **Chemical Reaction of Amines and Nitrite Salts**

   Formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines and nitrite salts under acidic reaction conditions. Under these conditions, nitrite salts may form nitrous acid, which can react with an amine to form a nitrosamine (see Figure 1). There is a greater risk of nitrosamine formation if nitrous acid is used to quench residual azide (a reagent commonly used in

tetrazole ring formation or introduction of azide functional group into a molecule) in the presence of precursor amines.

Amines may be present in a manufacturing process for a variety of reasons. The API (or API degradants), intermediates, or starting materials may contain secondary or tertiary amine functional groups. Tertiary and quaternary amines may also be added intentionally as reagents or catalysts. All of these types of amines can react with nitrous acid or other nitrosating agents to form nitrosamines.

2. Contamination from Raw Materials

Nitrosamine impurities can be introduced when vendor-sourced materials, including starting materials and raw materials, are contaminated.

- Nitrosamine contamination has occurred when fresh solvents (ortho-xylene, toluene, and methylene chloride) were contaminated during shipment from vendors (e.g., during transfer between storage vessels).
- Sodium nitrite is a known impurity in some starting materials (such as sodium azide) and may be present and react with amines under acidic conditions to form nitrosamines. Nitrate-containing raw materials, such as potassium nitrate, may contain nitrite impurities. The amount of nitrite impurity that can be tolerated is process dependent and should be determined by each API manufacturer.
- Secondary or tertiary amines have been reported as impurities in some raw materials and in fresh solvents such as toluene.
- Starting materials or outsourced intermediates may be at risk through cross-contamination if they are manufactured at sites where nitrosamine impurities are produced in other processes.

3. Recovered Solvents, Catalysts, and Reagents as Sources of Contamination

Recovered materials such as solvents, reagents, and catalysts may pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine). If the recovery process involves a

quenching step (i.e., nitrous acid used to decompose residual azide), nitrosamines could form during solvent recovery. These nitrosamines may be entrained if they have boiling points or solubility properties similar to the recovered materials, depending on how recovery and subsequent purification takes place (e.g., aqueous washes or distillation). This further increases the risk of contamination in material recovery.

4. Quenching Process as a Source of Nitrosamine Contamination

There is a risk of nitrosamine formation when a quenching step is performed directly in the main reaction mixture (i.e., when nitrous acid is added to the reaction mixture to decompose residual azide). This allows nitrous acid to come into direct contact with residual amines in the raw materials used in the manufacturing process. The nitrosamine impurities could be carried to the subsequent steps if there are not adequate removal or purification operations in place, or if the operations are not optimized for removing specific impurities of concern. This can contaminate the entire downstream process once they are introduced. Even if the quenching process is conducted outside of the main reaction mixture, there is a risk if contaminated recovered materials are introduced into the main process.

5. Lack of Process Optimization and Control

Another potential source of formation of nitrosamine impurities is lack of optimization of the manufacturing process for APIs when reaction conditions such as temperature, pH, or the sequence of adding reagents, intermediates, or solvents are inappropriate or poorly controlled.

6. Environment and Water

N-nitrosamines occur and are formed in the environment. In the air they form mainly by combustion processes and in water by biological processes in trace amounts. NDMA can occur in drinking water as it is a by-product of several industrial processes and is a contaminant of certain pesticides. NDMA has recently been identified as a disinfection by-product of chloramination (by the reaction of

monochloramine with dimethylamine, a ubiquitous component of waters impacted by wastewater discharges) and, to some extent, chlorination. NDMA can also be formed as a by-product of anion-exchange treatment of water. It is generally removed during water treatment by UV irradiation. The current WHO Guideline "Guidelines for drinking-water quality" (WHO/HSE/AMR/08.03/8; 4th edition, incorporating the 1st addendum) defines a limit for NDMA in drinking water of 0.1 µg/L , equivalent to 0.1 µg/kg = 0.1 ng/g = 0.1 ppb in case of ρ = 1 kg/L, due to different sources from the environment.

Control strategies are according to the as low as reasonably achievable (ALARA) or as low as reasonably practicable (ALARP) principles. Concentrations are considered to be higher in areas with less control and high air and water pollution.

Acceptable Intake Limits

FDA recommends the following acceptable intake (AI) limits for the nitrosamine impurities[1]:

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

[1] The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA,NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. Appendix B includes a description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.
[2] The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

Reduction and Prevention of Nitrosamine Impurities

The following strategies to mitigate the presence of N-nitrosamines in human medicinal products should be considered[1,2,3]:

- Strive for designing / adapting manufacturing processes to prevent the formation of or contamination with N-nitrosamines.
- Risk assessment of route of synthesis, starting materials, intermediates, raw materials (solvents, reagents, catalysts, etc.) and finished product manufacturing process (raw materials, packaging etc.) in consideration of the potential and confirmed root causes for the formation and contamination of N-nitrosamines in API synthesis and in finished product.
- In case of identification and confirmation of any risk for the presence of N-nitrosamine through testing, a change of manufacturing process, starting materials and intermediates, raw materials or primary packaging in order to avoid use of nitrosating agents should be considered.
- If combination of nitrosating agents with solvents, reagent and catalysts have been justified to be unavoidable in the entire process, adequate control measures should be implemented. This must be reflected in the control strategy of the API and finished product as appropriate.
- The control point for nitrosamines should be selected in such a way that it will give assurance of presence of the impurity below the acceptable limit in the finished product.
- ICH M7(R1) provides the option for skip testing, which can be applied also in the case of a single nitrosamine impurities, as long as it can be shown that levels of the single mutagenic impurity in the drug substance are consistently less than 30% of the ICHM7(R1) limit for the respective N-nitrosamine, and provided the root cause of a detected nitrosamine is well-known and well-controlled.

  For details of reduction and prevention strategy, you can read the guidelines mentioned in the references.

Conclusion

Nitrosamine impurities are genotoxic and carcinogenic agent. The presence of nitrosamines in human medicinal products shall be mitigated as much as possible and shall be at or below the limit based on ICH M7(R1) principles for substances to manufacture safe medicine for the patients.

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