Joint MHLW/PMDA-USP Workshop “Role of Quality in Pharmaceuticals”

Session 4 Impurities: Mutagenic impurities and more

Control of nitrosamine impurities in sartan drugs

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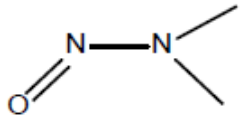
Disclaimer

Views expressed in this presentation are solely of the speaker and do not necessarily represent those of the PMDA.

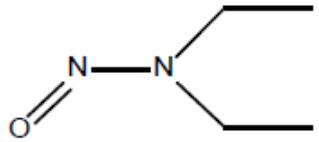
Nitrosamines

Nitrosamines are classified as probable or possible human carcinogens and referred to as “cohort of concern” compounds in the ICH M7 (R1) guideline.

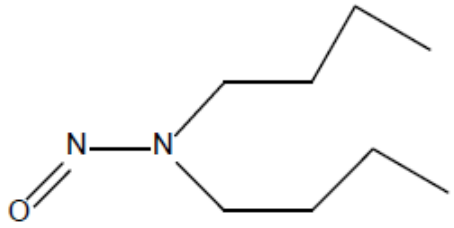
Examples of nitrosamines



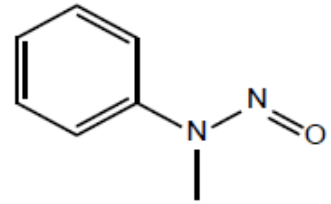
N-Nitrosodimethylamine (NDMA)



N-Nitrosodiethylamine (NDEA)

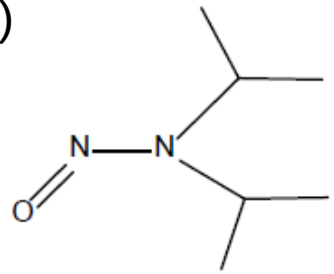


N-Nitrosodibutylamine (NDBA)

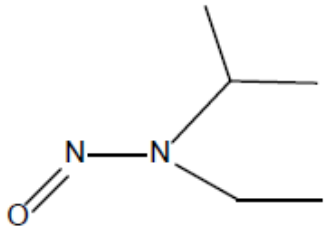


N-Nitrosomethylphenylamine (NMPA)

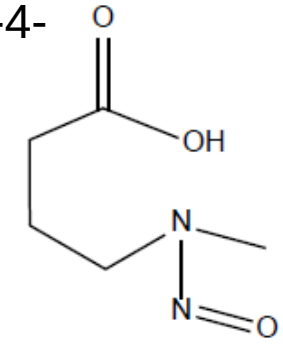
N-Nitrosodiisopropylamine (NDIPA)



N-Nitrosoisopropylethylamine (NIPEA)



N-Nitroso-N-methyl-4-aminobutyric Acid (NMBA)



Acceptable intake limits

The AI limit is a daily exposure to a nitrosamine impurity that approximates a 1:100,000 cancer risk after lifetime exposure.

The AI limits may be updated based on additional information.

Nitrosamine	AI limit (µg/day)
NDMA	0.0959
NDEA	0.0265
NDBA	0.0265
NDIPA	0.0265
NIPEA	0.0265
NMBA	0.0959

Voluntary recalls in Japan

July 5, 2018
VALSARTAN Tablets 20 mg, 40 mg, 80 mg, 160 mg
“AA”
- Containing valsartan API manufactured by Zhejiang Huahai Pharmaceuticals Co., Ltd.

February 7, 2019
AMVALO Combination Tablets “Pfizer”
- NDEA levels above the recommended AI limit and the detection of NDMA

September 26, 2019 -
RANITIDINE Tablets 75 mg, 150 mg (9 companies)
RANITIDINE Injection 50 mg, 100 mg (3 companies)
- The detection or possibility of the presence of NDMA

October 23, 2019
NIZATIDINE Capsules “OHARA”
- NDMA levels above the recommended AI limit

April 27, 2020
METGLUCO Tablets 250 mg, 500 mg
METFORMIN HYDROCHLORIDE Tablets 500 mg
MT “JG”
- NDMA levels above the recommended AI limit

September 16, 2020
METFORMIN HYDROCHLORIDE Tablets 500 mg
MT “TOWA” / “NICHIIKO”
- NDMA levels above the recommended AI limit

April 26, 2021
METFORMIN HYDROCHLORIDE Tablets 500 mg
MT “JG”
- NDMA levels above the recommended AI limit or possibility of the presence of NDMA

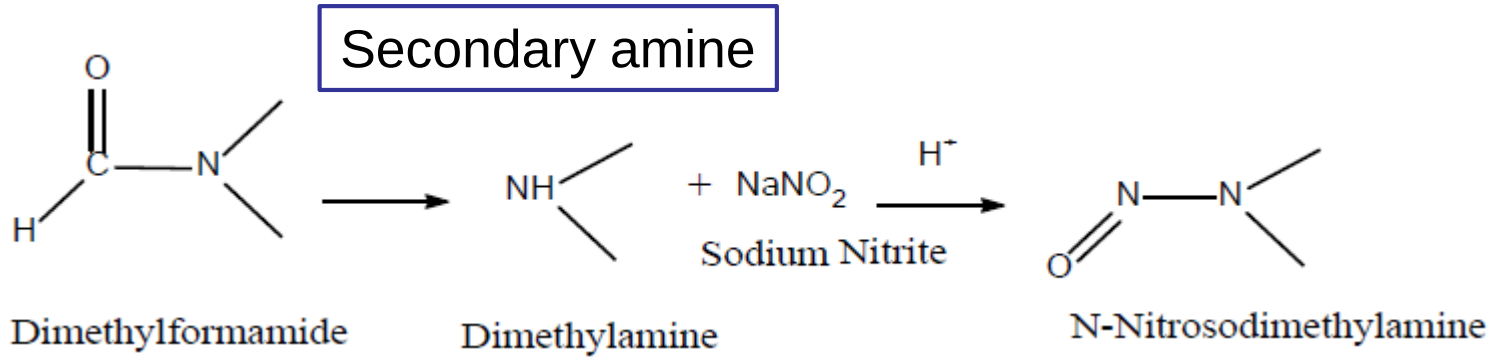
Root causes

Formation of nitrosamines is possible in the presence of secondary or tertiary amines and nitrites under acidic conditions.

- API processing under the presence of secondary or tertiary amines and nitrites (e.g., sartans).
- Some drug products may degrade during storage, resulting in the formation of nitrosamines (e.g., ranitidine?) .
- Excipients or container-closure system may contain amines and potential sources of nitrosating agent (e.g., metformin?) .

Formation of nitrosamines in sartan drugs

e.g. NDMA



Amine source	NOx source	Nitrosamine
N,N-dimethylformamide (DMF)	Sodium nitrite ($NaNO_2$)	NDMA
N-methylpyrrolidone (NMP)		NMBA
Triethylamine (TEA)		NDEA
Diisopropylethylamine (DIPEA)		NDIPA
		NIPEA
Tetrabutylammonium bromide (TBAB)		NDBA

Risk assessment in sartan drugs

1. Sources of secondary and tertiary amines

- If the reactions are performed at high temperatures in solvents with high boiling points (e.g., DMF, NMP) to speed up reactions, these amid solvents can degrade into secondary amines.

  ➡ React with nitrous acid to form nitrosamines (e.g., NDMA, NMBA).

- Tertiary amines (e.g., TEA, DIPEA) and quaternary ammonium salts (e.g., TBAB) used as reagents may contain secondary and tertiary amines.

  ➡ React with nitrous acid to form nitrosamines (e.g., NDEA, NDIPA/NIPEA, NDBA).

✓ Nitrosamine impurities vary depending on the raw materials used in the manufacturing process.
✓ In many cases, there is a risk of forming two or more nitrosamines.

Risk assessment in sartan drugs (continued)

2. Presence of sodium nitrite

- Sodium nitrite is a known impurity in sodium azide, which is often used for synthesizing tetrazoles.
- An aqueous solution of sodium nitrite is used to quench residual azide, but sometimes omitted from reaction schemes and the process description in CTD module S.2.2.
- Nitrites used as reagents in one step (incl. starting materials) can carry over into subsequent steps, despite purification operations, and react with secondary or tertiary amines to generate nitrosamine impurities.

✓ The manufacturing processes of the starting materials should also be included in the risk assessment.

Risk assessment in sartan drugs (continued)

3. Recovery of raw materials

- Nitrosamine impurities may be concentrated in the recovery of raw materials (e.g., solvents, reagents, and catalysts).
- Recovery of raw materials is often outsourced to third-party contractors.

  Case studies

  - *O*-xylene and toluene were contaminated during recovery due to inadequate cleaning and to use of shared storage equipment between different customers.
  - The catalyst tri-*N*-butyltin chloride was contaminated at a third-party contractor facility due to the combination of this catalyst from different customers.

Analysis and control of nitrosamines in sartan drugs

- Manufacturers of APIs and drug products should use methods with limits of quantitation (LOQs) at or below 0.03 ppm.
- Given existing uncertainties regarding nitrosamine impurities and their presence in drugs, for at-risk APIs, testing of each batch on release should be conducted.
- If there is a risk of forming multiple nitrosamine impurities, total nitrosamine impurities should also be limited.
- Alternate approaches (e.g., upstream test of an intermediate) may be accepted based on sufficient process understanding.

Thank you for your attention.