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BLOCKING NITROSAMINES FORMATION IN DRUG PRODUCTS

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LEGAL NOTIFICATION

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TOPICS

- Introduction to Nitrosamines
- Historical Background
  - Occurrence of Nitrosamines
- Origin of Nitrosamine Impurities in Human Drugs
- Control of Nitrosamine Iimpurities in Human Drugs
- Future Direction of Research
- Conclusion

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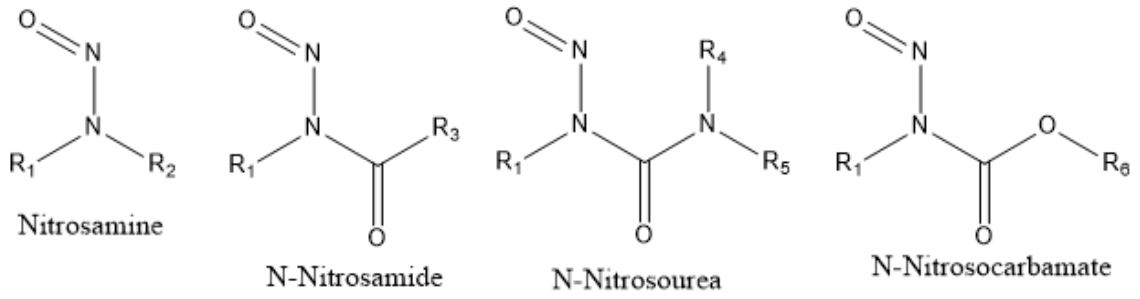
INTRODUCTION TO NITROSAMINES

- Nitrosamines are a family of carcinogens which are formed by the reaction of **secondary/tertiary amines, alkyl derivatives of amides/ carbamates/urea** with nitrite or other nitrogenous agents with the nitrogen in the +3 state.
- Classified by ICH M7 Guidance as Class 1 impurities – “known mutagenic carcinogens”
  - ❖ *Based on both rodent carcinogenicity and mutagenicity data*
- Categorized by the International Agency for Cancer Research (IARC) as 2A – Probable Carcinogens and 2B – Possible Carcinogens



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OCCURRENCE OF NITROSAMINES

The all-pervasive nature of the amines and the nitrosating agents (nitrites, nitrates, oxides of nitrogen) make nitrosamines a common class of impurities in the human environment

Some of the most well-known exogenous sources of nitrosamines:

- Tobacco (smoking and chewing)
- Rubber products
- Cosmetics like creams, lotions, shampoos
- Metal cutting fluids
- Nitrosamines are also present in food such as bacon, beer, and preserved fish. They can be formed when red meats are heated to high temperatures
- Drinking water (WHO, 2008, EPA 2016)
- **Impurities in Pharmaceuticals**

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ORIGIN OF NITROSAMINES IMPURITIES IN HUMAN DRUGS

- Nitrosamines can be present as impurities in drugs based on one or more of the following factors:
  - Drug Substance
    - Reagents used in manufacturing the drug substance
    - Regulatory Starting Materials
    - Intermediates
    - Solvents including Water
    - Cleaning Agents and shared equipment
  - Drug Product
    - Drug Substance (amine prone to nitrosation)
    - Excipient (nitrite/nitrate, amines)
    - Extraneous source of nitrite/nitrate (packaging, solvents, water, equipment contamination)

CONTROL OF NITROSAMINE IMPURITIES IN HUMAN DRUGS

- Control of nitrosamines in Drug Substance:
  - Based on the current knowledge of the chemistry of nitrosamines, understanding of the route of synthesis of the drug substance, it is relatively easier to apprehend and control nitrosamines in drug substance.
- Controls of nitrosamines in Drug Product
  - It is difficult to apprehend and mitigate the risk of nitrosamines in the drug product when the origin of nitrosamine impurity is not the API
  - Especially at risk are drug products where the drug substance is an amine, capable of nitrosation
  - Excipients may be a source of nitrate/nitrite which can react with amines
  - Excipients are sometimes 90% or more of the formulation
  - Excipients are not manufactured under cGMP conditions
  - Most excipient manufacturers do not test the excipients for nitrite/nitrate or small amines

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CONTROL OF NITROSAMINE IMPURITIES IN HUMAN DRUGS

Challenges with controlling nitrosamines in the drug products

- Several drug substances are secondary, tertiary amines and capable of forming the corresponding nitrosamines in presence of nitrite/nitrate and other nitrosating agents in the drug product.

- A high-level review of the drug substances present in finished drug products approved by FDA for human use and have monographs in the United States Pharmacopeia showed the following:

  - Number of Drugs with dimethylamino groups (alerts for NDMA formation) **~65**
  - Number of Drugs which are secondary amines which can form N-nitrosamines **~95**
  - Number of Drugs which are tertiary amines and thus can form N-nitrosamines **~135**
  - Number of Drugs which are quaternary amines and thus can form N-nitrosamines **~10**

- When the drug substance is a secondary amine, the possibility of formation of nitrosamine corresponding to the drug substance is very high in presence of nitrites/nitrates (nitrates may reduce to nitrites in presence of reducing agents and trace metals):

HOW TO MITIGATE THE NITROSAMINES IN HUMAN DRUGS

Drug Product Related Considerations

- In order to avoid formation of nitrosamines in drugs, amines and/or nitrites/nitrosating agents need to be absent from the formulation
- It is impossible to get rid of secondary, tertiary and quaternary amines in finished dosage forms as they are common reagents and constitute a large part of the drug substances in approved drugs
- Thus, the best way to prevent formation of nitrosamines in finished dosage forms is to cut down the source of nitrite/nitrate
- It would be worth exploring the feasibility of adding trapping agents capable of scavenging adventitious nitrosating agents including nitrites and nitrates in drug product formulations.
  - Potential nitrite scavengers as inhibiters of formation of nitrosamines may include chemicals like ascorbic acid, caffeic acid, ferulic acid, phenolic acids, resorcinol, glutathione

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FUTURE DIRECTIONS OF RESEARCH

- There needs to be changes in research orientation – not much work has been done on nitrosamines since 1990s due to lack of grants in this area.
  - Toxicology of many nitrosamines need to be revisited
- The Acceptable Intake (AI) of the nitrosamines need to re-evaluated
- Initiatives should be taken to study the mechanism of prevention of nitrosation
  - Nitrosation can be prevented by effectively quenching nitrites or by slowing the process of formation of nitrosamines using inhibitors

How can FDA help?

In addition to developing sensitive methods, revisiting the toxicology of nitrosamines, FDA may support research related to prevention of nitrosation

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CONCLUSION

The best way to mitigate the risk of nitrosamines in pharmaceuticals may be the prevention of these impurities being formed rather than attempting to tighten their specifications in drug products and drug substances to impractical levels

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Thank you!