GENOTOXIC IMPURITIES IN PHARMACEUTICALS: THE CASE OF NITROSAMINES

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Introduction

Nitrosamines (NAs) (Figure 1) are recognized genotoxic impurities frequently detected in pharmaceutical products, associated with significant mutagenic and carcinogenic risks in humans.

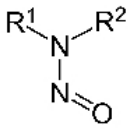

Figure 1

Objectives

This study aimed to systematically review national and international publications from 2019 to 2023 regarding the identification, risk assessment, and control strategies for NAs in active pharmaceutical ingredients (APIs) and finished pharmaceutical products, in alignment with the ICH M7 guideline.

Methods

An integrative literature review was performed across the Scielo, ScienceDirect, PubMed, and Web of Science databases using the keywords "genotoxic AND mutagenic impurities AND nitrosamines." Eligible studies included original research articles and review papers focusing on in silico, in vitro, or in vivo assays, published in English or Portuguese. Exclusion criteria encompassed book chapters, studies outside the specified time frame, analytical method validation reports, and studies addressing non-NA genotoxic impurities.

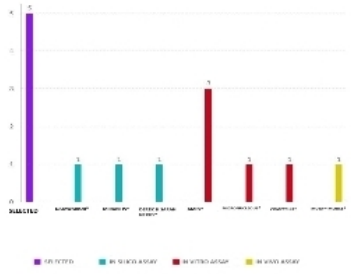

Figure 2

Results

Among the 107 articles initially identified, only five met the eligibility criteria. Three studies employed in silico prediction platforms (DataWarrior®, Mirabilis®, Derek Nexus®, and Sarah Nexus®) (Figure 2), while two studies utilized experimental approaches, including the Ames test, CometChip assay, and Muta™Mouse model (Figure 3). The results emphasized the critical need to validate in silico mutagenic alerts through experimental in vitro and in vivo assays. Furthermore, the findings underscored the importance of a three-tiered risk assessment approach (risk evaluation, confirmatory testing, and control measures) and the establishment of acceptable intake limits based on TTC values or compound-specific carcinogenicity data

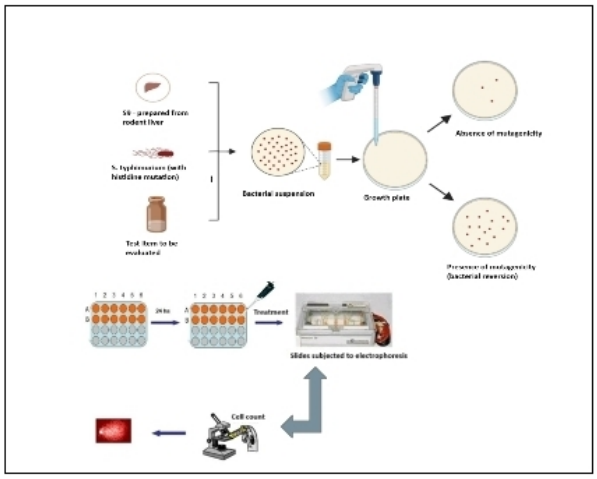

Figure 3

Conclusions

The findings stress the need to validate in silico mutagenic alerts experimentally, adopt a three-tiered risk assessment approach, and establish intake limits based on TTC or carcinogenicity data. The limited studies highlight the urgency for further research to improve risk mitigation and protect public health.

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