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The Risk of Cancer Correlated with Nitrosamine Exposure

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KEYWORDS

Nitrosamines, carcinogenesis, mitigate, nitrites or nitrates, tumor, genotoxicity, tumorigenic properties.

ABSTRACT:

The nitrosamines are a class of carcinogenic compounds that have garnered significant attention due to their association with an increased risk of various cancer types. More than thirty nitrosamines are on California's Proposition 65's list of substances that can cause cancer. Commonly used medications for the treatment of heartburn, hypertension, and type 2 diabetes have recently been contaminated with nitrosamine, which has led to multiple recalls by the US Food and Drug Administration (FDA). Among chemicals and within a particular species of laboratory animal, these nitrosamines share target tumor sites for their common genotoxic and tumorigenic properties. Sometimes the drug valsartan is used to estimate the additional cancer risks associated with NDMA (N-nitrosodimethylamine) and NDEA (N-nitrosodiethylamine) contamination. These estimates are based on nitrosamine levels reported by the US FDA, cancer potencies developed by California's Proposition 65 program and the US Environmental Protection Agency (EPA), and specific exposure scenarios. These estimates indicate that long-term drug use may raise the risk of cancer due to nitrosamine contamination, which is a major public health concern. The purpose of this thorough analysis is to clarify the connection between nitrosamine exposure and the onset of cancer.

INTRODUCTION

Nitrosamines are potent carcinogens due to their ability to cause DNA damage, mutations, and alterations in cellular pathways, culminating in uncontrolled cell growth and tumor formation.[1] One unique aspect is their potential to form in the stomach when certain foods, especially those high in nitrates or nitrites (like processed meats), are consumed alongside amines or amides. Gastric conditions, such as low stomach acid, may further increase nitrosamine formation. This localized generation of nitrosamines within the stomach lining can potentially elevate the risk of stomach cancer.[2] Additionally, nitrosamines can also be absorbed through the skin, which raises concerns about occupational exposure and the potential risks associated with certain cosmetics or industrial applications.[3]

Nitrosamines are chemical compounds that can form in certain conditions, particularly in processed or preserved foods, tobacco products, and some industrial processes.[4] Numerous medical organizations, including the International Agency for Research on Cancer (IARC), have classified these compounds as carcinogenic. Nitrosamines have been linked to different types of cancer, including stomach cancer, esophageal cancer, and certain types of liver cancer.[5] The formation of nitrosamines often occurs in foods that contain nitrites or nitrates, which are commonly used as preservatives, especially in processed meats like bacon, ham, and sausages. Smoking tobacco is another significant source of nitrosamine exposure. Reducing exposure to nitrosamines involves minimizing the consumption of processed meats, choosing nitrosamine-free products, and adopting healthier lifestyle choices like avoiding smoking. Regulatory measures and industry practices also aim to limit nitrosamine formation in various products to mitigate associated health risks.[6]

METABOLISM

The metabolism of nitrosamines plays a crucial role in their carcinogenic effects, particularly in the context of cancer development. Upon ingestion or inhalation, nitrosamines undergo metabolic activation and bioactivation processes within the body, contributing to their genotoxic and carcinogenic potential.[7] The

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metabolism of nitrosamines primarily occurs in the liver through a series of enzymatic reactions, predominantly involving cytochrome P450 enzymes (CYPs) and other metabolic pathways.[8] Initially, nitrosamines undergo cytochrome P450-mediated activation, leading to the formation of reactive intermediates, such as alkylating agents and free radicals. These reactive metabolites have the propensity to interact with cellular DNA, resulting in the formation of DNA adducts. These adducts can induce mutations by causing alterations in the genetic code or interfering with normal DNA replication and repair mechanisms.[9] Cancer may start and spread as a result of persistent DNA damage and mutations in important genes involved in cellular proliferation and regulation. Moreover, the metabolic pathways of nitrosamines can lead to the generation of reactive oxygen species (ROS) and other oxidative stress-related molecules. These reactive species can cause cellular damage by oxidizing cellular components, including lipids, proteins, and DNA, thereby promoting inflammation and contributing to the carcinogenic process.[10] The metabolism of nitrosamines and their subsequent activation into reactive intermediates is a critical step in their carcinogenicity. Understanding these metabolic pathways provides insights into the mechanisms underlying nitrosamine-induced carcinogenesis. Efforts to inhibit or modulate these metabolic processes may offer potential strategies for cancer prevention or therapeutic interventions. Research endeavors continue to focus on elucidating the intricate metabolic pathways of nitrosamines and their association with cancer development, aiming to identify biomarkers, therapeutic targets, and preventive measures to mitigate the adverse effects of nitrosamine exposure on human health.[11]

MECHANISM OF ACTION

Nitrosamine-induced carcinogenesis is caused by a complex mechanism of action that includes multiple processes that are involved in the development, propagation, and advancement of cancer.[12] Nitrosamines exert their carcinogenic effects primarily through genotoxicity, inducing DNA damage and mutations, disrupting cellular signaling pathways, and promoting tumor development.[13]

- DNA Damage and Mutagenesis: Nitrosamines are metabolically activated in the body, leading to the formation of reactive intermediates, including alkylating agents and free radicals.[14] These reactive species can interact with cellular DNA, forming DNA adducts and causing alterations in the genetic code. This DNA damage, if not properly repaired, can result in mutations within critical genes involved in cellular growth regulation, DNA repair, and apoptosis. These mutations can initiate carcinogenesis by disrupting normal cellular functions and promoting uncontrolled cell proliferation.[15]
- Formation of DNA Adducts: Nitrosamines generate DNA adducts through their interaction with nucleophilic sites in DNA molecules.[16] These adducts can impede normal DNA replication and transcription processes, leading to the accumulation of genetic abnormalities and increased genomic instability. Persistent DNA adducts and subsequent errors in DNA repair mechanisms contribute to the accumulation of mutations, a hallmark of cancer development.[17]
- Oxidative Stress and Reactive Oxygen Species (ROS) Generation: Metabolic activation of nitrosamines can also lead to the generation of reactive oxygen species (ROS) and other oxidative stress-related molecules. ROS can cause cellular damage by oxidizing cellular components, including DNA, proteins, and lipids. This oxidative stress induces inflammation, DNA damage, and cellular dysfunction, further contributing to the carcinogenic process and tumor progression.[18,19]
- Disruption of Cellular Signalling Pathways: Nitrosamines may interfere with various cellular signalling pathways involved in cell growth, differentiation, and apoptosis. They can dysregulate key signalling molecules and pathways, such as those related to cell cycle control and apoptosis (e.g., p53, Bcl-2 family proteins), promoting cell survival and proliferation, and inhibiting programmed cell death.[20,21]

The cumulative effects of DNA damage, mutations, oxidative stress, and disruption of cellular signalling contribute to the initiation and progression of cancer following exposure to nitrosamines. Understanding

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these complex mechanisms is crucial in identifying potential targets for cancer prevention, early detection, and therapeutic interventions.[22]

GENOTOXICITY

Genotoxicity refers to the capacity of certain substances to cause damage to genetic information within cells, leading to mutations, chromosomal abnormalities, or other changes in the DNA structure. Nitrosamines, a class of compounds known for their genotoxic properties, exert their effects through various mechanisms that can contribute to cancer development.[23]

- DNA Adduct Formation: Nitrosamines metabolically transform into reactive intermediates, such as alkylating agents or free radicals. These reactive species can bind covalently to DNA molecules, forming DNA adducts. These adducts alter the structure and sequence of DNA, potentially disrupting DNA replication, transcription, and repair processes.[24]
- Induction of DNA Damage: Nitrosamines can cause various types of DNA damage when they interact with cellular DNA, including strand breaks, base modifications, and cross-linking. This DNA damage can cause genomic instability and DNA repair errors, which can result in mutations in critical genes involved in cellular regulation.[25]
- Mutagenesis and Chromosomal Aberrations: The presence of DNA adducts and DNA damage induced by nitrosamines can lead to mutations in key genes that control cell growth, differentiation, and apoptosis. Additionally, these genotoxic effects can cause chromosomal abnormalities, such as deletions, translocations, or rearrangements, further contributing to cancer initiation and progression.[26]
- Oxidative Stress and Secondary Genotoxicity: Metabolism of nitrosamines generates reactive oxygen species (ROS) and other reactive molecules, leading to oxidative stress. ROS-induced damage to DNA can initiate additional genotoxic effects, exacerbating DNA strand breaks, base modifications, and cellular oxidative damage, thereby promoting carcinogenesis.[27]

The genotoxic effects of nitrosamines play a pivotal role in the initiation and development of cancer by causing genetic alterations that drive aberrant cell growth and survival. Understanding these genotoxic mechanisms is crucial for assessing the risks associated with nitrosamine exposure and devising preventive strategies to mitigate their carcinogenic potential.[28]

PREVENTION OF NITROSAMINE CARCINOGENESIS

One strategy for preventing cancer is to reduce human exposure to these carcinogens, and success has been achieved in many cases, despite the fact that exposure to nitrosamines in tobacco products is still too high. Nitrosamines can also be introduced into the body through the nitrosation of amines, which can happen when an acid or bacterial catalyst reacts with nitrite, or when amines react with nitric oxide products produced during infection or inflammation. Inhibiting this endogenous nitrosamine formation is a second strategy for preventing nitrosamine carcinogenesis. Significant decreases have been attained using ascorbic acid and additional nitrite absorbers. The basic metabolic activation step that cytochrome P450 mediates for nitrosamines is essential to their carcinogenic potential. Using chemopreventive drugs to obstruct this or other stages in the carcinogenic process is the third strategy. Strong chemopreventive agents against the carcinogenesis of nitrosamines have been identified. As an illustration of this strategy, chemoprevention of lung cancer caused by the tobacco-specific nitrosamine 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is covered.[29,30]

DISCUSSION

Using the carcinogenesis of nitrosamine as an example. There are many strong carcinogens in the class nitrosamines. Roughly 300 distinct nitrosamines have been linked to cancer. Preformed nitrosamines can be inhaled by humans through the food, in some work environments, and from using tobacco, cosmetics, medications, and agricultural chemicals.[31] Since nitrosamines are strong genotoxic carcinogens, NDMA, NDEA, NMBA, and the larger class of NMAs shouldn't be found in drugs in significant amounts. The rubber

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sector has been associated with the highest recorded levels of nitrosamine exposure in humans.[32] It's possible that nitrosamines contributed to the increased risk of pharyngeal, oesophageal, and bladder leakage. Frequent consumption of nitrosamine-containing foods, particularly NDMA, has been linked in non-occupational studies to a higher risk of oral cancer, according to a case-control analysis. Using cancer potencies created by the US EPA and California's Proposition 65 program, the range of cancer risks connected to these two nitrosamines. The estimated number of cancer cases per 100,000 individuals exposed to NDMA varied from 40 to 126. Although the presence of nitrosamines in food has been reported on a number of occasions, more recent analytical methods using mass spectrometry and gas chromatography have suggested that food nitrosamine levels may be lower than previously thought. It is talked about how food can form nitrosamines from nitrite and secondary amines, and how the body can form them especially in the stomach after food is consumed.[33] Lastly, some additional potential sources of nitrosamines in the environment are taken into consideration along with a review and brief evaluation of analytical techniques. Given that nitrosamines are metabolized identically in animal and human tissues, it appears highly probable that nitrosamines can cause cancer in humans.[34,35]

CONCLUSION

Key conclusions regarding the risk of cancer correlated with nitrosamine exposure include: Carcinogenic Potential: Nitrosamines exhibit potent carcinogenicity due to their ability to induce DNA damage, mutations, and genomic instability. Nitrosamines that have been metabolically activated form reactive intermediates that interact with DNA, leading to genetic alterations that initiate and promote carcinogenesis. Epidemiological Links: Epidemiological studies consistently demonstrate a correlation between increased exposure to nitrosamines and elevated incidences of specific cancers. Populations with higher consumption of nitrosamine-contaminated foods or increased exposure through tobacco smoke exhibit higher risks of stomach, esophageal, liver, and lung cancers. Mechanistic Pathways: Nitrosamines induce genotoxic effects by forming DNA adducts, causing DNA strand breaks, and initiating oxidative stress through reactive oxygen species. These mechanisms disrupt cellular functions, promote inflammation, and create a microenvironment conducive to cancer development. Targeted Prevention and Regulation: Efforts to mitigate nitrosamine exposure involve public health initiatives, dietary recommendations, and regulatory measures. Strategies include advocating healthier lifestyle choices, reducing processed meat consumption, avoiding tobacco use, and implementing regulations to limit nitrosamine levels in consumer products. The wealth of scientific evidence supports the significant association between nitrosamine exposure and the heightened risk of cancer. Understanding the mechanisms underlying nitrosamine-induced carcinogenesis is crucial for developing effective preventive strategies, regulatory policies, and public health interventions aimed at minimizing exposure and reducing the burden of cancer associated with nitrosamines.

DECLARATION OF INTEREST: None

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest in this study. The authors are responsible for the content and writing of the papers.

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