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Brief Report

Contamination of Food by Nitrosamines and the Associated Public Health Risks

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The presence of N-Nitrosamines (N-NAs) in food poses a serious risk to public health, according to a recent scientific opinion by the European Food Safety Authority (EFSA).[1,2] These genotoxic compounds, which induce liver tumours in rodents, are found in various food categories, with 'meat and meat products' being the main contributor to dietary exposure.[1-3] The EFSA assessment revealed that the Margin of Exposure (MOE) for the 10 carcinogenic N-NAs (NDMA, NMEA, NDEA, NDPA, NDBA, NMA, NSAR, NMOR, NPIP, and NPYR) in food was highly likely to be less than 10,000 for all age groups, indicating a significant health concern.[1-3] However, the assessment was limited by uncertainties due to censored data and lack of information on some food categories. This highlights the need for continued monitoring of N-NAs in food and the implementation of mitigation measures to protect public health.

The CONTAM Panel of the European Commission has conducted a scientific evaluation of the human health risks associated with the presence of N-NAs in food.[1-3] N-NAs are formed in food through the reaction of nitrosating agents with amino-based substances under certain routine processing conditions (Figure 1). These compounds have been detected in various food products such as cured meats, processed fish, beverages, cheese, soy sauce, oils, processed vegetables, and human milk.[4,5] Heat treatment during food processing can also increase the levels of N-NAs, particularly in meat and fish products.[6,7] The CONTAM Panel has identified and characterized the hazards of 32 N-NAs, but the risk assessment was focused on 10 carcinogenic N-NAs found in food.[1] These compounds have been shown to be absorbed and distributed in the bodies of experimental animals, primarily to the liver but also to lungs, kidneys, and brain.[8,9] N-NAs are also known to cross the placenta, and fetal exposure to these compounds has been reported.[10,11] The distribution of N-NAs within the body and the extent of accumulation in different organs may vary depending on the specific compound, the route of exposure, and individual factors such as age, sex, and metabolic capacity.[12,13] Most N-NAs undergo metabolism by specific enzymes (Figure 2), which can lead to the formation of DNA adducts that may initiate carcinogenesis.[14,15] The liver plays a significant role in metabolizing N-NAs,[16-18] but extrahepatic distribution can also occur, especially when co-exposure to other substances (such as ethanol and nicotine) that affect these enzymes involved in metabolism of N-NAs. Hence alcohol consumption and smoking can significantly enhance the toxicity of N-NAs.[14,19,20]

The fate of N-NAs in humans is not well understood, although measurable levels of these compounds have been found in blood, gastric juice, urine, and milk.[21,22] The origin of these N-NAs is unknown, and it is unclear whether they are formed endogenously or come from food, prescription drugs and/or water sources.[1,23-25] Limited studies involving human volunteers consuming meals with known N-NAs content have shown that only trace amounts of the ingested dose were recovered in biological fluids, except when ethanol was co-administered.[26] Ethanol may decrease the hepatic clearance of certain N-NAs, similar to what has been observed in rodents.[27] The metabolism and activation of N-NAs in humans can vary from those in rodents, and different tissues in the human body, such as the gastrointestinal and respiratory tracts, have been shown to contribute to the bioactivation of N-NAs.[17,18,28] Studies have also demonstrated the genotoxic properties of N-NAs, particularly the acyclic volatile N-NAs (NDMA, NMEA, NDEA, and NDPA). These compounds can induce gene mutations in both bacteria (influencing the microbiome) and mammalian cells, leading to DNA adduct formation and potentially disrupting the gut-brain and gut-cardiac physiology.[29-31] The cyclic volatile N-NAs (NMOR, NPIP, and NPYR) have also been shown to be mutagenic, while the genotoxicity of other N-NAs is less well-studied. The genotoxic mechanisms of N-NAs are the underlying mode of action for their carcinogenic activity in animals, but other potential mechanism such as through influence on microbiome cannot be excluded. N-NAs are reported to induce tumour formation in various organs such as the liver, pharynx, oesophagus, stomach, respiratory tract, and lung in different mammalian species.[17,18,32,33] Epidemiological studies examining the association between dietary intake of N-NAs and cancer have limitations due to factors like selection bias, information bias, and confounding influencers.[34-36] Also estimating N-NAs intake from food frequency questionnaires, as reported in several studies, can lead to misclassification of exposure.[37,38] Additionally, these studies cannot establish tumour target sites and reference points for N-NAs due to limitations in study design and the presence

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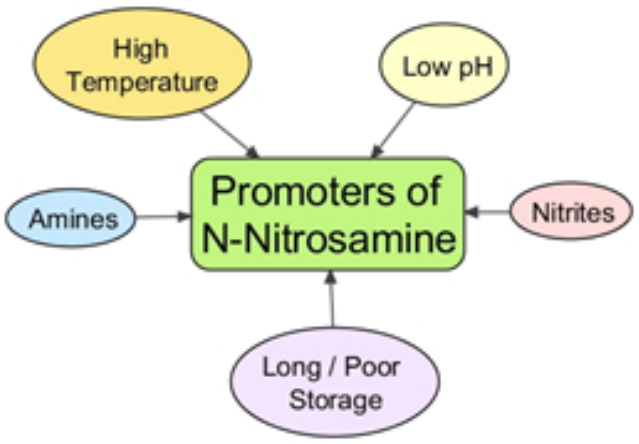

Figure 1: The most important factors that promote formation of N-nitrosamines (N-NA). N-NA formation increases with temperature (frying or grilling at high temperatures can increase the formation of N-NA in meat/protein rich products). Acidic conditions can promote the formation of N-NA (pickled vegetables or acidic juices contain higher levels of N-NA). Nitrites are commonly used as preservatives and curing agents in processed meats/frozen products. When nitrites are present in combination with amines or amides, they can form N-NA. Foods with high amine content, such as fish, cheese, and fermented products, may have higher levels of N-NA. Long / poor storage conditions can promote N-NA formation.

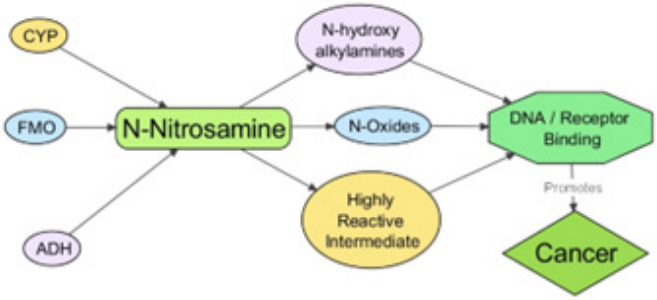

Figure 2: Enzymes involved in metabolism of N-nitrosamines. Cytochrome P450 (CYP), flavin-containing monooxygenase (FMO), and alcohol dehydrogenase (ADH) can metabolise N-nitrosamines. CYP enzymes are responsible for the initial activation of N-nitrosamines by converting them into highly reactive intermediates. FMO enzymes can also oxidize some N-nitrosamines to form their N-oxides, which are generally less toxic than the parent compounds. ADH enzymes can also metabolize N-nitrosamines to produce N-hydroxyalkylamines, which are further metabolized to form reactive intermediates. These reactive intermediates can then bind to DNA and other macromolecules, potentially leading to the development of cancer.

of other exposure sources and unmeasured factors. Nevertheless, the mutational signature of DNA adducts induced by N-NAs has been associated with the development of colorectal cancer, particularly with high intakes of processed or unprocessed red meat.[39,40]

The main food category contributing to N-NAs exposure is observed to be meat and meat products. The MOE ranged from 3,337 to 48 at the P95 exposure excluding some surveys with P95 exposure equal to zero. The EFSA CONTAM Panel concluded that the MOE for N-NAs at the P95 exposure is highly likely (98–100% certain) to be less than 10,000 for all age groups, which raises a health concern. Contamination of food by nitrosamines represents a significant public health risk (increasing prevalence of stomach and colon cancer), which should be mitigated by strategies such as, the reduction of nitrite uses in food and improved quality control solutions with collaborative inputs from the food industry and regulatory agencies.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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