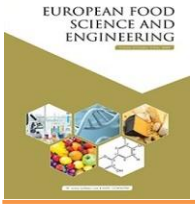

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Carcinogenic potential of food additives: A review

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ABSTRACT

Food additives are substances intentionally added to food to achieve specific technical or physical effects, such as reducing spoilage, enhancing colour, or improving flavour. This review focused on food additives with carcinogenic potential in humans or animals, as identified by the Food and Drug Administration (FDA) and the International Agency for Research on Cancer (IARC). Food additives benefit manufacturers, processors, and consumers, including acids that inhibit microbial growth and prevent foodborne diseases. Some commonly consumed foods and beverages contain compounds with carcinogenic potential in animal models. Furthermore, human exposure to several of these compounds has been associated with increased cancer risk. This review examined the role of food additives in dietary consumption, their classification as direct or indirect additives, and their potential ecological impacts. It highlights the importance of rigorous safety assessment and regulation of food additives to protect public health, considering both the benefits and potential risks associated with their use in the food industry.

1. Introduction

Food risk components (FRCs) provide worldwide challenges. Skill impediments threaten community well-being and the pliability of the food system (Jin et al., 2020, Zhang et al., 2020). FRCs comprise anthropogenic and biogenic substances, including pesticide residues, environmental contaminants, illicit or hazardous additions, and biogenic food toxins (Shi et al., 2024). The World Health Organisation (WHO) estimates that food contaminated with FRC leads to disease in 1 in 10 individuals, leading to 420,000 fatalities per year (Wicker et al., 2016). Global industrialisation and resultant environmental pollution, including industrial wastewater discharge, metal mining and smelting, pesticide application, and solid waste accumulation, have controlled an increase in the detection of anthropogenic pollutants in food, particularly with the introduction of FRCs (Wang et al., 2020).

A principal pathway for anthropogenic contaminants to infiltrate food crops and livestock occurs when agricultural activities are conducted near pollution sources, such as contaminated soil from adjacent industrial operations or irrigation utilising polluted water (Adnan et al., 2022). Extensive education has established the detrimental effects of pesticide remains on soil, worldly, and water ecosystems, as well as optimistic associations with the danger of neurological and generative disorders and cancer. Additionally, veterinarian medication remains have been shown to induce hearing loss, liver and kidney harm, disrupt microbial balance, and have carcinogenic properties (Carvalho, 2017, Thompson et al., 2017, Bacanlı & Başaran, 2019). Infants and toddlers are particularly vulnerable to these foodborne pathogens. Extended exposure to these chemicals may lead to detrimental health consequences, including developmental problems (Mielech et al., 2021). Adults and immunocompromised individuals constitute a height-risk demographic for foodborne infections because of various variables, including reduced resistant classifications, long-lasting conditions, and the consequent elevated risk of problems (Thaivalappil et al., 2020).

In addition to anthropogenic contaminants, biogenic poisons in flora and fauna and those produced by fungi and bacteria pose significant risks to human health. Mycotoxins, which are minor deadly metabolites synthesised primarily by fungi of the genera Aspergillus, Alternaria, Fusarium, and Penicillium, lead to the adulteration of nutrition, vegetables, and fruits (Tian et al., 2022). Bacterial toxins consist of poisonous particles, polypeptides, and proteins generated by bacteria that can disrupt cell membranes and the extracellular matrix (Kuzmenkov et al., 2016). Edible plants may also harbour specific poisonous metabolites, for example, glycoalkaloids in potatoes and aristolochic acid in fish mint,

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which can result in liver and kidney failure along with additional well-being hazards (Kemprai et al., 2023). Furthermore, specific peptides and proteins found in animal crops can delay the functions of essential enzymes, ion channels, and receptors in human digestion, compromising homeostasis and adversely affecting the nervous and cardiovascular systems (Akbarian et al., 2022). This review focuses on food additives with carcinogenic potential in humans or animals, as identified by the Food and Drug Administration (FDA) and the International Agency for Research on Cancer (IARC).

2. Food and Beverages

Foods and beverages are fundamentally intricate combinations of substances ingested for nourishment or enjoyment. The diversity of compounds included in food is extensive, as are their differing qualities (Kobets et al., 2022). Substances exhibiting carcinogenic activity in rat models have long been identified in numerous regularly consumed foods. The complexity of food safety and quality arises from diverse sources such as flora, microbes, contaminants, additive applications, and reactions that transpire during processing, cooking, and storage (Jackson, 2000, Blandino et al., 2003).

Additionally, carcinogens may be generated endogenously from dietary constituents (Tricker & Preussmann, 1991, Rietjens et al., 2022). It fails to consider that drinking water toxins like arsenic, the effects of caloric content and macronutrients, for instance, overweight, or the overconsumption of intoxicating drinks, altogether of which have been related to heightened cancer dangers in people (Pflaum et al., 2016, Key et al., 2020).

The carcinogenic mechanism of action (MoA) is strongminded by chemical construction. DNA-reactive carcinogens possess structures that produce reactive electrophiles, either directly or after undergoing bioactivation. In contrast, epigenetic carcinogens do not have these properties but feature structures that interact with additional molecular and cellular mechanisms that are critical to cancer development (Williams et al., 2014, Kobets et al., 2019). These disparities in MoA highlight the hazards of human cancer due to exposure (Williams, 1997, Williams, 2008).

3. Food and Cancer

Food is ingested for its nutritional benefits and sensory gratification, including flavour and fragrance. The United States (US) food system guidelines rely on future applications within specific food categories, demographic consumption groups, and projected health claims associated with those items. Direct or indirect food substances may only be lawfully introduced if the manufacturer has proven free from harmful qualities under designated use circumstances (Rolls, 2015). A novel product or component might be classified as a direct food preservative or a generally recognised safe (GRAS) component; however, its purpose may be uncertain regarding its incorporation into food or its influence by hereditary and ecological issues. A substance designed to provide colour upon addition or application to food is controlled independently as a colour additive (Pressman et al., 2017).

Cancer is a multifactorial disease influenced by genetic and environmental factors. Nutrition contributes to the elevated incidence of cancer. The characteristics, ingested quantity, and additive composition of dietary products may be significant in the potential incidence of cancer. Consuming refined carbohydrates may help the growth of colon cancer (Chan & Giovannucci, 2010). Excessive eating of red meat might raise the risk of colon cancer (McAfee et al., 2010). Additional variables contributing to elevated cancer risk stem from the chemicals incorporated into processed foods (Belpoggi et al., 2006, Mueller et al., 2010, Bastide et al., 2011).

4. Food Additives

Food additives are substances intentionally added to food products to achieve specific desirable effects, for example, enhancing flavour, appearance, and shelf life (Ukwo et al., 2022). They are primarily used in processed foods and are not typically consumed on their own (Sadler et al., 2021).

Food additives are essential in the food industry, encompassing direct additives deliberately added to food for specific effects and indirect additives that may migrate from packaging materials. With thousands of additives developed to enhance food safety, convenience, and nutrition, their regulation and safety assessment are paramount for public health protection (Zang & Kabadi, 2001). These additives serve various functions, including sensory enhancement, nutrient fortification, processing aid, and preservation, with different categories like colourants, sweeteners, vitamins, and antioxidants (Alekseeva et al., 2022, Owusu-Apenten & Vieira, 2022). Additionally, food hydrocolloids, including polysaccharides and proteins, are widely employed as thickening agents, stabilisers, and delivery transporters for bioactive compounds, offering health benefits and varied requests in food and biomedicine productions (Kutlu et al., 2020, Kutlu et al., 2021, Lu et al., 2021). The emergence of nutraceuticals, functional foods, and supplements further highlights the evolving landscape of food research to address health concerns and develop alternative therapies (Ditu et al., 2018). Food additives can be categorised into many classifications according to their functionality (Table 1).

4.1. Role of food additives in dietary consumption

All individuals must consume food! The human diet consists of different biochemical compounds, primarily of natural origin, and intentionally added components such as nutrients, colourants, and flavour enhancers. During processing and food preparation, additional chemicals may be incorporated into food, resulting in chemical alterations and the introduction of molecules not typically present in raw agricultural items (Pressman et al., 2017). Chemicals are additionally used to attain positive practical effects, including colouration, preservation, constancy (e.g., emulsification), flavour enhancement, sweetener, and other physical alterations. Supplementary compounds are frequently incorporated, typically in minimal quantities, primarily as byproducts of cultivation and packaging. These may include pesticides, pharmaceuticals utilised in livestock organisations, and chemicals that leach from food interaction of packaging surfaces (FCSs) (Marone et al., 2016, Pressman et al., 2017).

Table 1. Main types of food additives and their uses with examples

Food additives	Examples	Uses
Nutritional additives	Examples include vitamins A, D, and B vitamins, vitamin C, essential fatty acids, minerals like calcium and iron, and dietary fiber (Pogorzelska-Nowicka et al., 2018)	Used to restore nutrients lost during processing or enrich foods to correct dietary deficiencies (Augustin et al., 2016)
Processing agents	Examples include anticaking, bleaching, clarifying, emulsifiers, leavening, humectants, PH control, and stabilisers/thickeners (Abdulmumeen et al., 2012)	Used to aid in processing or maintaining desired product consistency (Chandan, 2015)
Preservatives	Examples include salt, spices, sulfites, benzoates, sorbates, propionates, and nitrites (Silva & Lidon, 2016)	Used to prevent spoilage and extend shelf life (Mei et al., 2019)
Sensory agents	Examples include flavouring agents, flavour enhancers, and colourants (Ramesh & Muthuraman, 2018)	Used to enhance taste, aroma, or appearance (Lesme et al., 2020)

The human diet also includes several undesirable pollutants from natural sources, including bacteria and their metabolites and chemicals inherent to plants (Kruger et al., 2014, Pressman et al., 2017). The Food Additive Alteration near the Federal Food, Drug, and Cosmetic Act (FDCA) mandated regulatory oversight of food additives. It empowered the FDA to request evidence from manufacturers showing that the additive posed minimal risk before its incorporation into the food source. The Food and Drug Administration (FDA) defines the kinds of poisonousness and chemical assessments necessary to evaluate the care of food additives and Generally Recognized as Safe (GRAS) substances. The safety evaluation standards for food additives and compounds undergoing (GRAS) appraisal match. The primary distinction is in the period to market and then the qualifications of professionals assessing the readily accessible protection information (Roberts, 1981).

4.2. Direct and indirect food additives

A substance anticipated to be incorporated into food qualifies as a food additive. It requires premarket approval from the FDA without being deemed Generally Recognised as Safe (GRAS) through competent specialists or falls under other exclusions specified by the FDCA. Since 1958, additives have been the focus of food additive petitions that succumbed to the FDA (Noah & Merrill, 1998, Mosley, 2014). Petitions must include suitable protection data to enable the agency to fulfil its approval standards. Substances incorporated into food intended for a detailed function are recognised by way of ‘’direct additives’’ and are listed and arranged as the component marker of the respective food product. Aspartame, a low-calorie sweetener, is an intentional ingredient in puddings, yoghurt, soft drinks, and other food products. An indirect additive integrates into the food in minimal quantities during processing, storage, or packaging (Adhikari, 2021).

Additives fulfil important practical roles, including preserving the nutritional integrity of food (Kruger et al., 2014), improving stability or quality, hence decreasing food waste (Roberts, 1981), enhancing consumer appeal (FDA, 2014) and offering necessary assistance during processing. Currently, many compounds occur in the food consumed in the US, most of which are manufactured by manufacturers. Indirect additives are required by law to disclose their concentrations in food when they approach levels that may lead to discernible negative effects. Despite direct and indirect food additives, dispensation assistances are not obligatory to be listed on the element declaration (Kwon et al., 2023).

4.3. Ecological impacts of food additives

A food additive may remain interested in the released surroundings through its production and application. Taste sensations experienced through eating or drinking can spread through the environment through manure systems. Chemicals utilised to produce food additives might also be incorporated into wastewater treatment, industrial, or processing facilities (Pressman et al., 2017). Alternative pathways for introducing food additives encompass landfill solid waste disposal, food processing, and solid waste combustion. The National Environmental Policy Act (NEPA) mandates that the FDA evaluate its regulatory actions' environmental consequences (1985). Petitioners must conduct an environmental evaluation before FDA approval of a FAP (Gibbs & Kahan, 1986). Addressed issues encompass the proposed application of physical and chemical properties. Metabolic grade about ecological fate in air, utilisation, soil, and water; anticipated ecological attentions; potential toxicological impacts on water and global organisms; and ecological ramifications of production and final disposal. Introduction levels and environmental fate absorption rates and soil are assessed to forecast the maximum attentiveness of the additive in related ecological media (Cousins et al., 2002).

After feasible, developments manipulating the transportation and alteration of food additives are utilised for predicting ecological concentration. Relevant data encompass chemical constancy, biodegradability, and movement in waste media (oil sorption, water volatility, and solubility) (Kahrilas et al., 2015). Following the estimation of the material released into the atmosphere, the ecological assessment entails a review of existing data regarding toxicity to fauna, flora, and other organisms within the environmental section (terrestrial ecosystems, air, estuarine, lake, and maritime) at the ecosystem level. The toxicity database is thereafter analysed alongside the degree of ecological contact to evaluate potential threat (Lytle & Lytle, 2001).

5. Food Additives and Carcinogenesis

Food additives undergo toxicologic assessments meant for safety assessment. Additives scientifically and officially validated as safe are permitted for usage in the food industry. However, using about processed meals comprising specific

food additives hawthorn increases the hazard of human cancer (Table 2), despite adherence to the regulatory limitations for these compounds in such meals. Recent research reveals that processed meat containing preservatives like nitrite and nitrate elevates the risks of colorectal and pancreatic cancer (Bastide et al., 2011, Larsson & Wolk, 2012). Consumption of soft drinks like Coke may elevate the risk of some cancer types, as demonstrated by the research (Belpoggi et al., 2006). This study had rats maintain a typical diet during their lifespan, with one group receiving regular tap water and the other group receiving Coke as their drinking water source. The prevalence of breast cancer in women and pancreatic cancer in females and males was elevated in the collection consuming expel compared to the group receiving typical water discharge (Qadir et al., 2024). A comparable study indicated that consuming beverages with food additives may elevate tumour danger. The study shows that 600 Singaporeans who consumed two or more glasses of non-alcoholic beverages weekly for 14 years exhibited an increased incidence of pancreatic cancer, while no similar evidence was found among those who drank fruit juices (Mueller et al., 2010).

Food additives are incorporated into food to enhance or preserve specific attributes, including texture, flavour, appearance, or safety. Several substances are directly incorporated into foods, whereas others infiltrate foods in minimal quantities during storage, handling, or packaging (FDA, 2010). FDA rules from the late 1950s prohibit the addition of any direct food additive with carcinogenic possible to food. However, contemporary understandings of the various mechanisms of biochemical carcinogenesis call the validity of these regulations into question (Williams et al., 1996; Krishan et al., 2021).

In Japan, madder colour produced from the roots of *Rubia tinctorum* (madder root) is used in food colouring. In a carcinogenicity investigation, F344 rats nursed a regime covering *Rubia tinctorum* colour excerpt for 104 weeks and significantly higher renal and liver cell carcinoma rates in mutual sex activity. The *Rubia tinctorum* colour excerpt was banned from usage in 2004 (Inoue et al., 2009) because of carcinogenic findings, combined through its high genotoxicity, yet its present IARC categorisation remnants Cluster 3. In systematic research, a metabolite of a *Rubia tinctorum* colour constituent has been revealed to produce a significant character in carcinogenicity (Inoue et al., 2009). Potassium bromate is an oxidising substance commonly used as a food ingredient, particularly in bread-making. Potassium bromate causes renal cell cancer in pests (Kurokawa et al., 1983, DeAngelo et al., 1998). Potassium bromate has both initiating and promoting properties in swine kidney carcinogenesis. Its potency in pests appears lower than that of rats with hamsters. In contrast to its modest genotoxicity in microbiological studies, potassium bromate had a relatively high ability to cause chromosomal abnormalities. The consequences of 8-hydroxydeoxyguanosine synthesis in the rat kidney suggested that reactive oxygen species produced by potassium bromate were responsible for its hazardous and carcinogenic impacts (Sai et al., 1992).

These cases illustrate that certain processed foods with approved ingredients may elevate the risk of carcinogenicity despite the absence of any publicly proclaimed safety concerns regarding these compounds. Consequently, one may hypothesise the following causes for the potential carcinogenicity of certain chemicals in food crops. No carcinogenic concerns were established in investigational trials examining alterations in food structure, potential adverse synergistic effects from additional carcinogenic compounds in flavourings, prolonged exposure due to poor storage conditions, or the possibility of exceeding acceptable limits (Felter et al., 2021).

Table 2. Food additives promote carcinogenicity at high exposure doses

Food additives	Cancer types
Cyclamic acid and its Na and Ca Salts	Colon and hepatocellular tumours, Prostate adenocarcinoma, Thyroid and Uterus adenomas (Takayama et al., 2000)
Allura Red AC	Colon tumor (Tsuda et al., 2001)
Acesulfame potassium	Urinary tract tumour (Andreatta et al., 2008)
Aspartame	Urinary tract tumours (Soffritti et al., 2007), Lymphoma, leukaemia, and breast tumours (Ter Veld et al., 2006)
BHA(Butylated hydroxyanisole)	Breast tumour (Lu et al., 2002, Qadir et al., 2024)
BHT(Butylated hydroxytoluene)	Bladder tumour (Saito et al., 2003), Lung tumour (Plesner & Hansen, 1983)
Hexamethylenetetramine	Adrenal gland pheochromocytoma and Harderian gland tumour (Mahapatra & Parija, 2018)
Carboxymethyl cellulose, Sodium carboxymethyl cellulose	Fibrosarcoma at the side of subcutaneous injection (Uittamo et al., 2011)
Xylitol	Adrenal medulla tumour (Cross et al., 2010)
Nitrates, Nitrites	Colorectal cancer and Bladder tumour (Ferrucci et al., 2010), non-Hodgkin lymphoma (Kilfoy et al., 2010), Thyroid tumour (Kilfoy et al., 2011), Brain (Preston-Martin et al., 1982), Hepatocellular tumour (Sayed-Ahmed et al., 2010), Advanced prostate cancer (Sinha et al., 2009)
Propionic acid and salts	Fore stomach tumour (Harrison, 1992)
Saccharin and its salts	Bladder tumour (Tisdel et al., 1974), Thyroid tumour (Prasad & Rai, 1986)
Talc	Adrenal gland and lung adenoma/carcinoma (NTP, 1993) Endometrial cancer (in genital usage of women as talcum powder) (Karageorgi et al., 2010)
Polyoxyethylene stearate	Bladder papilloma (Shubik, 1975)
4-Hexylresorcinol	Adrenal gland pheochromocytoma and Harderian gland tumor (Chhabra et al., 1988)

6. Potential Factors Contributing to the Development of Additive Carcinogenicity

6.1. Structural changes

When food additives interact with other food components, their chemical structure may alter due to physical, chemical, or enzymatic activities. Nitrites and nitrates are transformed into nitrosamines in meat crops (SIDS, 2005). The primary nitrosamines current in meat and dairy foodstuffs of crops are

N-nitrosodimethylamine and N-nitrosopyrrolidine. In Belgique, 101 thirsty agitated sausages were analysed for remaining sodium nitrate and nitrite concentrations, biogenic amines, and volatile N-nitrosamine levels. The findings revealed that N-nitroso morpholine and N-nitroso piperidine were present in a notable percentage of samples (22% and 28%, respectively) (Catsburg et al., 2014, De Mey et al., 2014), and observed the part of dietetic bases of N-nitroso compounds (NOCs) and NOC precursors as potential risk factors for bladder cancer in a situation-regulator training performed in Los Angeles. The intake of treated meats, such as pastrami, corned beef, salami, and liver, which contain amines and nitrosamines, was meaningfully related to a heightened risk of bladder cancer.

6.2. Adverse synergistic effects

The influence of the interaction among various food additives on carcinogenicity may have been neglected in assessments of their individual carcinogenic risks. The risk may have been exacerbated by a food ingredient that elicited an adverse reaction. Scientific evidence exists to substantiate this hypothesis. The mixture of potassium sorbate, ascorbic acid, and ferric or ferrous salts has demonstrated mutagenicity and DNA-damaging effects, but their individual use does not exhibit such activity (Kitano et al., 2002). A different study investigated the synergistic impact of a combination of six prevalent reproduction food colourants (allura red, brilliant blue, new cocaine, erythrosine, tartrazine, and fast green) on the poisonousness of the carcinogen 3-amino-1,4-dimethyl-5H-pyrido[4,3-b] indole (Trp-P-1) utilising primary refined swine hepatocytes, demonstrating that the food colourant combination heightened the cytotoxicity of Trp-P-1 (Ashida et al., 2000).

7. Various Safe Chemicals may be Associated with Cancer

As per the International Agency for Research on Cancer (IARC), approximately the additives are deemed safe because they present no significant risk level (NSRL) despite a minimal cancer risk. Only permissible quantities are sanctioned for human ingesting. ‘’All additives’’ referenced in this document are deemed harmless after ingested within permissible amounts. Consequently, the factors above may have compromised the safety of certain chemicals, potentially elevating their carcinogenic effects or hazards, particularly in processed food (Cohen & Ito, 2002, Gultekin et al., 2015).

7.1. Mechanisms of carcinogenicity of DNA-reactive carcinogens

DNA-reactive carcinogens possess characteristics that facilitate the development of electrophilic reactants, which can covalently attach (adduct) to nucleophilic sites in nuclear DNA and other macromolecules, such as RNA and proteins, within the board tissues of carcinogenicity (Miller & Miller, 1981, Hartwig et al., 2020). Inboard tissues, only DNA reactant may produce multiple DNA adducts at distinct nucleophilic places on the same dishonourable before across bases. The pace of repair for each adduct may differ depending on its chromosomal position. The global reparation scheme controls adducts in cutting-edge transcriptionally inactive regions, whereas the transcription-coupled repair mechanism deals with adducts in transcriptionally lively areas (Hanawalt et al., 2003). The concentration of DNA adducts from exposures is determined by various parameters, including contact incidence, dosage, and the effectiveness of DNA overhaul used for exact adducts. Respectively, adduct has a unique ability to induce mutations, especially at base-pairing sites, which are extra mutagenic. ‘’Pro-mutagenic DNA alterations’’ develop into changes through cellular repetition (Fuchs, 2002). Changes in key growing regulatory genetic factors cause neoplastic transformation and progression (Vogelstein et al., 2013).

‘’DNA-reactive carcinogens’’ may also induce other biological effects, including cytotoxicity, which can promote increased cell proliferation and donate to their carcinogenic potential (Poirier, 2012). DNA-reactive carcinogens may exhibit cumulative effects within their board structures. Specific DNA adducts do not result in carcinogenicity, as adducts are present where cancer formation does not occur after food administration (Poirier & Beland, 1994, Poirier, 2012). Acrylamide, as mentioned below, generates adducts in both non-target and target tissues (Doerge et al., 2005). Epigenetic changes may be necessary for neoplastic conversion induced by specific adducts (Lafferty et al., 2004, Pavanello et al., 2009).

DNA-reactive carcinogens are generally genotoxic in test techniques that accurately depict the necessary bioactivation due to DNA interactions (Williams et al., 1996, Preston & Williams, 2005, Phillips & Arlt, 2009). Furthermore, DNA-reactive carcinogens frequently induce cancer at many locations and with brief exposure periods, even following the administration of a single dosage in some examples. This feature underpins their engagement in restricted ‘’short-term bioassays’’ (Williams et al., 2014). Several DNA-reactive carcinogenic agents remained identified as lacking observable detrimental impact levels (NOAELs) for carcinogenic belongings popular visceral replicas (Neumann, 2009, Williams et al., 2012), despite the existence of contradictory data. It is clear that biological verges potentially affect the probability of cancer growth for genotoxic carcinogens, according to the phases of carcinogenesis. Currently, criteria for DNA-reactive carcinogens are not widely accepted from a risk assessment and organisation position (Adeyeye, 2020).

7.2. Carcinogenicity mechanisms of epigenetic carcinogens

Epigenetic carcinogens do not engage in chemical reactions with DNA (Williams, 1992, Pogribny & Rusyn, 2012). In the board matters of carcinogenicity, the mechanisms of the act of these carcinogens include molecular or cellular changes that may indirectly principal to alterations in DNA function or cellular behaviour through secondary pathways (Kobets et al., 2019). ‘’Epigenetic carcinogens’’ may persuade oxidative pressure, subsequent trendy oxidative DNA injury (Klaunig & Kamendulis, 2004, Pogribny & Rusyn, 2012), which may cause neoplastic alterations or increased cell propagation, easing neoplastic growth, frequently arising after cryptogenic pre-neoplastic cells. Epigenetic hazards can touch genetic factors, foremost toward neoplastic transformation. Epigenetic carcinogens may touch genetic factor appearance, foremost toward neoplastic transformation (Jones & Baylin, 2007, Baylin & Jones, 2016), like belongings, which are frequently particular to rodents.

Epigenetic carcinogens can augment the carcinogenic potential of ‘’DNA-reactive carcinogens’’ via interacting mechanisms, such as neoplasm advancement. Epigenetic carcinogens generally yield negative results in genotoxicity studies due to their absence of direct DNA responsiveness,

unlike DNA-reactive chemicals, even when bioactivation occurs, unless influenced by an artefact such as severe cytotoxicity that induces mutagenicity. Epigenetic drugs typically necessitate extended high-level exposures to manifest their carcinogenicity. Their mechanism of action indicates that in restricted bio-assays, they exhibit harmful results for starting action. However, they may demonstrate promising results for endorsing action (Williams et al., 2014). Epigenetic carcinogen agents stay recognised toward demonstrating NOAELs intended for the cellular effects that contribute to the carcinogenicity from bodily replicas (Williams, 2001, Kobets et al., 2019) by way of examining some foodborne carcinogens addressed in this article. Thresholds for DNA-sensitive hazards are typically acknowledged from a hazard valuation viewpoint (Adeyeye, 2020).

8. Establishing Interaction with Additional Carcinogenic By-products in Profitable Additives

Unknown substances may be present in certain foods, potentially posing a consumer risk. For example, after ammonium is utilised, unwanted by-products like 4-methylimidazole may be generated during caramel synthesis. The derivative of (4-methylimidazole) induces lung cancer in mutual females with male pests by elevated dosages and precipitates leukaemia in women (National Toxicology Program, 2007, Chan et al., 2008). Certain Coke crops were discovered to have raised stages of 4-methylimidazole in their honey ingredients, exceeding the no significant risk level (NSRL). On February 16, 2011, the Centre for Knowledge in the Community Interest initiated a public request urging the United States FDA to prohibit the use of these caramels in such products (Gultekin et al., 2015).

8.1. Insufficient and extended packing conditions

Inappropriate surroundings might cause an alteration in chemical construction. Benzoates, such as sodium, potassium, and calcium) benzoate and benzoic acid exemplify common cases. They may undergo decarboxylation reactions to produce a carcinogenic compound, benzene, in the presence of erythorbic acid and ascorbic acid under appropriate UV light, pH, or temperature conditions (Gardner & Lawrence, 1993).

8.2. Surpassing the permissible thresholds

Food additives are marketed only once their Acceptable Daily Intake (ADI) levels are officially determined. The permissible maximum quantity that may be incorporated in foods is established to meet these ADI limits. Nevertheless, foods covering chemicals are expended typically, resulting in sustainable production to satisfy market requests. Consequently, this legal stipulation for maximum limits may have been surpassed using standard production processes (Stanković & Ćirić, 2021).

Research examining the effect of micro-particles in Crohn's disease indicated that titanium dioxide microparticles were consumed in amounts surpassing the acceptable daily intake (ADI) (Lomer et al., 2002). A comparable study in Italy showed that the antioxidant BHT was ingested in quantities exceeding the ADI (Leclercq et al., 2000). Phosphorus consumption in the US has been shown to exceed the ADI standard (Calvo & Park, 1996). The nutritional intake of nitrite and nitrate from natural foods was evaluated in France. The study revealed that dietary nitrite intake exceeded the ADI threshold in 0.7%-16.4% of adults and 10.5%-66.2% of kids, correspondingly (Menard et al., 2008). In Estonia, the concentration of nitrite and/or nitrate in meat crops was evaluated, revealing that nitrite consumption surpassed the ADI standard by as much as 140% for kids old 1 to 6 years (Reinik et al., 2005). Research investigating the use of reproduction nutrition colours amongst 3,141 broods in Kuwait revealed that sundown yellow, tartrazine, carmoisine, and Allura red were ingested in quantities exceeding the acceptable daily intake (ADI) (Toledo et al., 1992, Husain et al., 2006).

8.3. Epigenetic carcinogen risk assessments

The role and significance of epigenetic mechanisms induced by dietary variables in human cancer development are uncertain (Herceg, 2007), and the optimal method for assessing the risk of such carcinogens continues to be a subject of contention (Braakhuis et al., 2018). However, at low intermittent dosages (below 1 mg per day), epigenetic Carcinogens be situated non carefully for tumour dangers on the way to persons (Williams, 2008). This might indicate the lack of analogous mechanisms in humans compared to rodents, such as (d-limonene alpha 2μ(α2μ)-globulin) nephropathy in male pests resulting in kidney cancer (Swenberg & Lehman-McKeeman, 1999), or the significantly lesser human contacts, demonstrated by forestomach prevention in rats induced by Butylated Hydroxyanisole (BHA) critical toward squamous prison cell carcinoma (Williams & Whysner, 1996). Furthermore, the reversibility of epigenetic alterations may mitigate potential human harm. Consequently, epigenetic Carcinogens (NOAELs) stay employed toward established care standards, including tolerated daily intake TDI (Williams, 2008).

8.4. Food-derived carcinogens risk assessments

Application of carcinogenicity data to human risk

Risk assessment utilises dual categories of carcinogenicity information, human epidemiological data, and cancer data derived from rodent model tests (IARC., 2009). The former is deemed more pertinent for several reasons (Barlow & Schlatter, 2010). However, such data frequently lack comprehensive human revelation information and may be inadequately regulated (Raffaele et al., 2011). Animal data are often more reliable; however, they often contain results with dubious relevance to humans (Raffaele et al., 2011, Edler et al., 2014). The tumorigenic effects entail mechanisms of action that operate solely in rats. Furthermore, rodent studies fail to replicate actual human exposure in terms of both attentiveness and incidence. The social diet has a combination of elements that promote and impede carcinogenicity. Therefore, by evaluating human hazards, binary factors be considered paramount: the mode of action of carcinogenicity and the human exposure dosage (Hartwig et al., 2020).

After identifying a chemical in a nutrition product and determining its structure, an in silico study can be conducted to assess the possibility of DNA reactivity based on structure-activity connections (Rosenkranz, 2004). Although this method is effective for comparatively simple chemicals, the intricacies of several accepted crops render the nuances of metabolic initiation progressively challenging to anticipate.

Table 3. Description of the risk assessment of chemical agents

Risk assessment of chemical agents	Description
Hazard identification	The determination of potential adverse health effects from exposure to a substance. This determination is based upon a review of the toxicity data, which includes toxicity testing results in experimental animals and any knowledge of effects on human health and the mechanism/mode of carcinogenesis (Chartres et al., 2019).
Hazard characterisation	Determining the dose-response relationship and relevance to humans, incorporating factors such as interspecies variation in susceptibility and the relevance of mode/mechanism of action to humans (Cohen Hubal et al., 2010).
Exposure assessment	The amount of human exposure to a substance is determined. This determination uses data collected on the contaminant levels in food and specific food intake (consumption) information to calculate probable human exposure (Moretto, 2015).
Risk characterisation	Exposure to a hazardous chemical poses an estimated risk to human health. This procedure can be used to conclude, for example, what level of exposure to the hazardous chemical is associated with an increase in carcinogenic risk, even if very small. In addition, the risk characterisation is used to inform risk managers what level of risk may be acceptable or tolerable. To arrive at these estimates, consideration is given to the toxicity profile of the chemical in question, mechanisms of action, relevance to humans, dose response, and potential human exposure (Tice et al., 2013).

When adequate physical remains obtainable, a straight challenge used for DNA responsiveness stands as the preferable method (IARC, 2009, Turner et al., 2023). Table 3 presents information on the organization of Carcinogens through administration activities and their carcinogenic strengths (TD50) derived from rodent tumorigenicity studies.

In contrast to pharmaceuticals, the FDCA does not mandate the acquisition of scientific protection information for food additives. The protection valuation method for food additives may rely exclusively on the outcomes of tentative investigations. When human data are accessible, they should be integrated into the protection outline of the food additive (Pressman et al., 2017). When substantial human consumption is anticipated, petitioners may want to perform human research following a comprehensive nonclinical examination (NRC, 2004). Clinical studies on specific macro ingredient food additives might be necessary, as excessive consumption of macro ingredients in rodents has demonstrated changes in normal physiology, resulting in misleading toxicological effects irrelevant to humans. Moreover, inquiries concerning the impact of elevated amounts of these additives on nutritional caloric gratified with the alteration of micronutrient homeostasis are most effectively addressed in humanoid subjects (Pressman et al., 2017, Reddy & Hayes, 2018).

Assessment of risks associated with DNA-reactive rodent carcinogens

On the way to assess potential care anxieties associated with the attendance of carcinogens that operate through DNA-reactive mechanisms in food, various controlling and optional organisations, including the European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM) and the Combined Food and Cultivation Organisation of the United Nations (FAO), WHO, JECFA, and MoE, employ specific methodologies (O'Brien et al., 2006, Benford et al., 2010). The Margin of Exposure (MoE) is intended using the relation amid a pertinent Fact of Parting for cancer reply; for instance, No Observed Adverse Effect Levels (NOAELs) found in beast studies and a projected or expected human revelation level (Edler et al., 2014, Paustenbach & Cox Jr, 2024).

9. Conclusion

This review underscores the dual nature of food additives, acknowledging their benefits in enhancing food preservation, sensory appeal, and processing efficiency while highlighting potential carcinogenic risks. While food additives play a crucial role in the modern food industry, rigorous safety assessment and continuous monitoring are paramount to safeguarding public health. The carcinogenic potential of certain additives, as identified by the FDA and IARC, necessitates a balanced approach that considers both the advantages and potential hazards associated with their use. Future research should focus on elucidating the long-term effects of food additive exposure, refining risk assessment methodologies, and exploring safer alternatives to ensure a secure and sustainable food supply.

Author's Contributions

The authors contributed equally. Amjad Mahmood Qadir: Conceptualization, Software and Resources, Tables, Revision and Supervision; Dastan Jamal Salih, Software and Resources, Tables. The authors have reviewed and consented to the published version of the manuscript.

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Conflicts of Interest

The authors disclose no conflicts of interest.

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