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Synthetic Antioxidants in Food and Pharma: A Comprehensive Toxicological Review of BHA, BHT, and TBHQ

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Abstract

The most commonly used synthetic phenolic antioxidants (SPAs) are butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tert-butylhydroquinone (TBHQ), which are widely used in food, pharmaceutical, and cosmetic industries to prevent lipid oxidation. Although they have long been regulated, new toxicological findings are casting doubt on the belief that these compounds are biologically inactive at allowable dosages. This review is a synthesis of existing information on the physicochemical and toxicokinetic properties and molecular actions of these additives. There is some evidence, though, that SPAs are metabolically activated to produce reactive intermediates, such as quinone methides and semiquinones, which cause oxidative stress, endocrine disruption, and immunotoxicity. According to bio-monitoring evidence, humans are widely exposed (much higher than dietary model estimates) and do accumulate in

the urine, serum, and breast milk. This review identifies the differences between international regulatory frameworks- especially between the EU and the US and the necessity of cumulative risk estimates that consider vulnerable groups, including children and pregnant women.

Introduction

Synthetic phenolic antioxidants like butylated hydroxy anisole (BHA), butylated hydroxytoluene (BHT), and tert-butylhydroquinone have long been used to prevent oxidative degradation in food, pharmaceuticals and cosmetics for over half a century. They have played a vital role in increasing the shelf life of lipid-rich products in processing, storage and distribution because of their efficiency, stability, and economical production costs (Shahidi & Zhong, 2010a). Given the current rise in global intake of processed and packaged foods, prolonged human exposure to these additives is almost inevitable, particularly in populations with high consumption of ready-to-eat or fried foods (de Oliveira et al., 2018). Toxicological data are mounting to challenge the long-held belief that these substances are biologically inert at the levels of consumption that are permissible (Umar et al., 2026a). Although BHA, BHT, and TBHQ can be used as antioxidants in a food matrix, they may be pro-oxidants in the body. As part of metabolic activation, they produce reactive intermediates that can lead to oxidative DNA damage, damage to proteins, and lipid damage (Bouayed & Bohn, 2010; Xu et al., 2021).

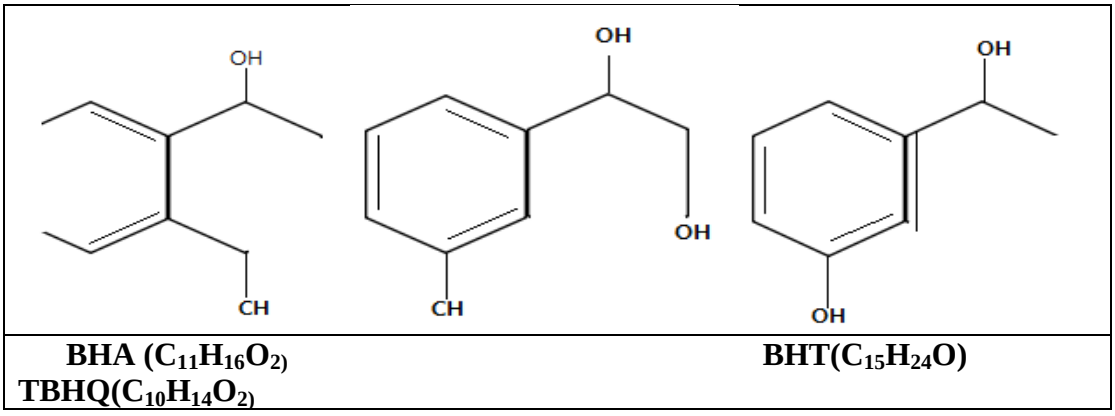
The International Agency for Research on Cancer (IARC) has listed BHA as a Group 2B carcinogen based on evidence in the tumorigenesis of experimental animals (Organization & Cancer, 1986). Moreover, quinone methides generated by BHT metabolism were associated with oxidative stress and hepatotoxicity (Gharavi & El-Kadi, 2005), despite TBHQ being demonstrated in both in vitro and in vivo studies as causing genotoxicity, immunomodulation, and endocrine disruption (Y.-L. Zhao et al., 2020). New biomonitoring data suggest that actual levels of exposure might be higher than conventional estimates found in diets. BHT and TBHQ metabolites were detected in human urine, serum, human breast milk, and fingernails, which proves that they have been considerably exposed to them (Ren et al., 2025). Children, pregnant women, and individuals with pre-existing metabolic or liver conditions may be at greater health risk due to both reduced metabolic clearance and relatively higher exposure per unit of body weight (Ren et al., 2025). The Acceptable Daily Intake (ADI) for TBHQ is set at 0.7 mg per kg of body weight, yet children often consume amounts that surpass this level, largely because they eat more food relative to their size (Ocagli et al., 2024). Those with existing liver issues are especially susceptible, as TBHQ affects biological pathways linked to non-alcoholic fatty liver disease (NAFLD) and triggers pro-inflammatory cytokines such as TNF, IL6, and IL1B that may worsen pre-existing conditions (Ren et al., 2025). Network toxicology studies further show that TBHQ interacts with key molecular targets like ACE, HIF1A, NR1H4, NFKB1, and ESR1, all associated with metabolic disturbances and impaired detoxification processes(Ren et al., 2025). Prolonged exposure beyond safe thresholds has also been linked to endocrine disruption and hormonal imbalances, raising particular concerns during pregnancy and early development (Barbouti et al., 2025). Also, food manufacturing and packing workers have had significantly higher urinary concentrations of these metabolites, suggesting that the exposures include more pathways than dietary intake (Fouda et al., 2022). The FDA allows the use of TBHQ, BHA, and BHT in U.S. food products, limiting them to no more than 0.02% of the oil or fat content (Beynen). In contrast, European authorities under the EFSA adopt a more cautious stance, noting that children—especially those consuming infant formula may be exposed to levels surpassing the recommended safe intake of 0.7 mg/kg of body weight(Additives & Food, 2016). The EU enforces clear concentration limits ranging from 25 to 400 mg/kg, while the FDA’s regulatory standards have

drawn criticism for being outdated (Petcu et al., 2023). This disparity has prompted new legislative efforts in the U.S., such as the proposed Food Chemical Reassessment Act of 2025, aimed at reexamining these additives, similar to actions already completed by European regulators. Similarly, Japan prohibits the use of BHA in infant food and restricts TBHQ levels in certain fat-containing products (Inoue et al., 2025). These inconsistencies highlight the need to align risk assessments that account for endocrine, immunological, and genetic effects.

Meanwhile, growing consumer demand for cleaner labels and natural preservation methods is pushing the industry toward plant-based antioxidants such as tocopherols, rosemary extract, and green tea catechin (Parveen et al., 2025). Despite their biological benefits and consumer appeal, challenges regarding efficacy, thermal stability, and sensory impact have driven interest in nanotechnology-based delivery systems to enhance stability and bioavailability (Ayala-Fuentes & Chavez-Santoscoy, 2021; Rafiq et al., 2025; Umar et al., 2026b). These advancements underscore the evolving landscape of antioxidant technology and raise new regulatory and safety issues (Aslam et al., 2025).

This research also evaluates natural and nano-enabled solutions to identify a pivotal knowledge gap toward the global acceptance of safer food and pharmaceutical systems aligned with Sustainable Development Goals (SDG 3, SDG 12).

Chemistry and Industrial Applications



BHA ($C_{11}H_{16}O_2$) **BHT($C_{15}H_{24}O$)**
TBHQ($C_{10}H_{14}O_2$)

Figure1. Structure of BHA, BHT. TBHQ

Synthetic phenolic antioxidants commonly used to prevent lipid oxidation include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tert-butylhydroquinone (TBHQ). Their action is to give away a hydrogen atom in their phenolic hydroxyl group to the free radicals, thus ending the series of oxidative degradation (Shahidi & Zhong, 2010a). These compounds exhibit a range of efficacy, industrial applications, metabolic, and environmental persistence, which are determined by their particular structural configurations. BHA is mostly a combination of two isomers (3-BHA and 2-BHA) and has a methoxy group, which stabilizes the phenoxyl radical by donating electrons. This characteristic makes BHA especially useful in the preservation of fats and oils in dry food products like cereals and snack foods (Reed, 2009). BHT has two bulky tert-butyl groups, which induce steric hindrance on the hydroxyl group. This drawback only reduces its reaction rate relative to BHA; however, it greatly improves long-term stability, which is why BHT is best used in hydrophobic materials like plastics, rubber, and cosmetics (Lanigan & Yamarik, 2002). TBHQ is a hydroxyl derivative of hydroquinone, which has two hydroxyl groups, which gives it better antioxidant properties and heat stability. It is the best antioxidant to use in high-temperature applications like frying oils, which form stable quinone products when oxidized, without producing off-odours that are

undesirable(Karamac & Amarowicz, 1997). These antioxidants are used industrially in direct relation to their physicochemical profiles. BHA is also used in packaging material, cereals, and baked goods in the food industry because it is volatile and can be used in low concentrations. BHT, due to its high lipophilicity, is usually used in snack food, margarine, and cosmetics (e.g., lipsticks, creams) in which long-term stability in dry systems is needed (Alnuqaydan, 2024). The TBHQ is the standard in the industry to protect against thermal degradation and rancidity of frying oils and fish oils. In addition to food, they are important stabilizers in polymers and pharmaceuticals, which inhibit the oxidative degradation of plastics and maintain the activity of active pharmaceutical compounds (Chib et al., 2020). Another common industrial procedure is the use of synergistic mixtures, especially BHA and BHT, which take advantage of the unique radical-scavenging kinetics to offer a greater protection at a lower concentration of each, within the regulatory limits, which is usually established between 100200 mg/kg (Steffensen et al., 2019). The consumer demand for clean-label products is the leading trend in the current market, and many manufacturers are transitioning to the use of natural ingredients such as tocopherols or rosemary extract instead of BHA and BHT (Galanakis, 2022). Still, the high thermal stability and affordability of synthetic antioxidants guarantee their further application in mixed system formats, usually in low concentrations of the synthetics alongside natural extracts to balance effectiveness and commercial attractiveness (Rodrigues et al., 2020). Future efforts are focusing on better delivery systems, like nanoencapsulation, to boost the thermal stability of natural antioxidants to possibly narrow the gap with synthetics. However, there are still environmental issues with BHT because it and its transformation products are often found in water, sediments, and biota, and these could be long-range transported and bioaccumulated, potentially affecting future regulatory decisions (Almuraee, 2025).

Table 1. Physicochemical Properties, Industrial Applications, and Regulatory Status of BHA, BHT and TBHQ.

Property	**BHA**	**BHT**	**TBHQ**
Chemical Formula	$C_{11}H_{16}O_2$(García & Ortiz, 2000)	$C_{15}H_{24}O$ (Dai et al., 2024)	$C_{10}H_{14}O_2$ (Van Esch, 1986)
Lipophilicity (Log P)	~3.3 (Liu et al., 2025)	~5.3 (Liu et al., 2025)	~2.7 (Liu et al., 2025)
Thermal Stability	Moderate; degrades with prolonged high heat(Santos et al., 2012)	Good; stable in heated fats (Dai et al., 2024)	**Excellent**; most stable for frying >190°C (Santos et al., 2012)
Primary Food Applications	Cereals, baked goods, animal fats, packaging (Nanditha & Prabhasankar, 2008).	Snack foods, margarine, cereals (Baumann, 2020)	**Frying oils**, instant noodles, crackers (Bhattarai, 2019)
Primary Non-Food Applications	Pharmaceuticals, packaging materials	**Cosmetics** (lipsticks, creams), plastics,	Packaging, industrial fats (Oromiehie)

Property	BHA	BHT	TBHQ
	(Singh et al., 2012)	rubber (Pastoukhova, 2025)	
Key Metabolic Feature	Metabolized to TBHQ, linking their toxicology (Ren et al., 2025).	Forms electrophilic quinone methide (BHT-QM) (Meier et al., 2007).	Undergoes redox cycling, generating semiquinone/benzoquinone (Ren et al., 2025).
Environmental Persistence	Moderate (Zhang et al., 2023)	**High**; frequently detected in water and biota (Liu & Mabury, 2020).	Moderate (Liu & Mabury, 2020)
Regulatory Limit (Food, Example)	≤ 150 mg/kg (individually or in combination) in EU (Additives et al., 2018).	≤ 150 mg/kg (individually or in combination) in EU (Additives et al., 2022)	≤ 200 mg/kg in US; not approved in EU (Maziero et al., 2001).

Molecular Pathogenesis and Toxicity.

Biological activity of BHA, BHT, and TBHQ is a result of the complicated interaction between the developed antioxidant activity of these compounds and their frequently adverse pro-oxidant and signalling effects in biology. In essence, these artificial phenolic acid compounds are hydrogen donors, which scavenge the lipid peroxyl radicals (ROO•) and end the autoxidation chain reactions, which underlie their use in the industry (Shahidi & Zhong, 2010a). But in physiological circumstances, this protective role may turn the other way. After metabolic activation, these compounds may change from antioxidants to pro-oxidants. TBHQ is more prone to this change because of its hydroquinone structure, which is involved in a pointless redox cycle. The peroxidases and cytochrome P450 enzymes oxidize it to a semiquinone radical and then to tert-butylbenzoquinone (TBBQ). NADPH-dependent reductases like NQO1, in turn, convert TBBQ back to TBHQ, a reaction that causes high levels of superoxide anion (O 2) to be produced, cellular NADPH to be depleted, and oxidative stress to become exacerbated. In the same manner, CYP2B6 and CYP2C19 are the two main enzymes that metabolize BHT to an electrophilic quinone methide (BHT-QM). This electrophile can react with cellular nucleophiles, such as glutathione (GSH), protein-histidine, and DNA-purines to form covalent adducts, thus compromising antioxidant defenses and resulting in macromolecular damage. BHA is also involved in this dynamic through metabolic O-demethylation by CYP1A2 to TBHQ to establish a common redox stress pathway (Lanigan & Yamarik, 2002). High internal concentrations in food matrices may interfere with cellular activity while maintaining protective effects due to duality. The dual antioxidant and pro-oxidant properties of BHA, BHT and TBHQ, as the redox-scavenging of these compounds at low concentrations and the production of redox-active metabolites at high concentrations. One of the effects of this pro-oxidant and electrophilic activity is the interference with important cellular signaling pathways. The three compounds are all strong activators of the Nrf2-Keap1 pathway, which is a key intermediary of cellular antioxidant response. Both TBHQ and BHT are converted to electrophilic metabolites (TBBQ and BHT-QM) that covalently modify critical cysteine residues (e.g., Cys151, Cys273, Cys288) of the Keap1 protein. Modification of these residues

results in the inhibition of Nrf2 ubiquitination and proteasomal degradation, Nrf2 stabilization and its nuclear translocation, where it binds the Antioxidant Response Element (ARE) and activates the expression of cytoprotective genes, such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1) (Ren et al., 2025). Although such transient up-regulation is a normal cell defense mechanism, prolonged Nrf2 activation can promote tumorigenic phenotypes, including cell survival, proliferation, and resistance to chemotherapy, and this is referred to as the dark side of Nrf2 (de la Vega et al., 2018).

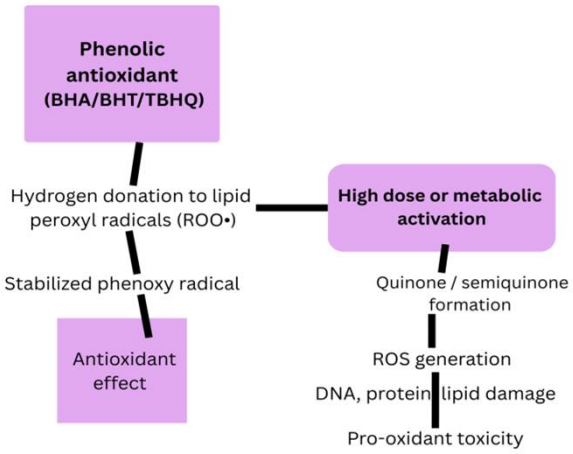


Figure 2. The dual antioxidant and pro-oxidant actions of BHA, BHT, and TBHQ illustrate their radical-scavenging mechanisms at low levels and the creation of redox-active metabolites at elevated concentrations.

The effect of these antioxidants on inflammation is dose-dependent. At moderate doses, TBHQ is able to suppress the activation of the NF- kB through stimulation of the Nrf2 pathway, and the effect is protective. It has been found that TBHQ can suppress the expression of certain NF-kB genes and reduce the levels of pro-inflammatory cytokines. However, at high concentrations or upon conversion to TBBQ, TBHQ could have some opposing effects, possibly by inducing pathways that increase pro-inflammatory cytokines or by inducing chronic inflammation in the setting of metabolic stress. Importantly, this duality implies that TBHQ cannot be categorised as pro-inflammatory (Khezerlou et al., 2022)

Recent in vivo research in cases of acute tissue damage, such as nephrotoxicity has shown that TBHQ can attenuate inflammatory response mechanisms that is, exert an anti-inflammatory activity. Finally, immunomodulatory actions of TBHQ depend on the dosages, biological model, and co-stressors (Whisel & Rice, 2025).

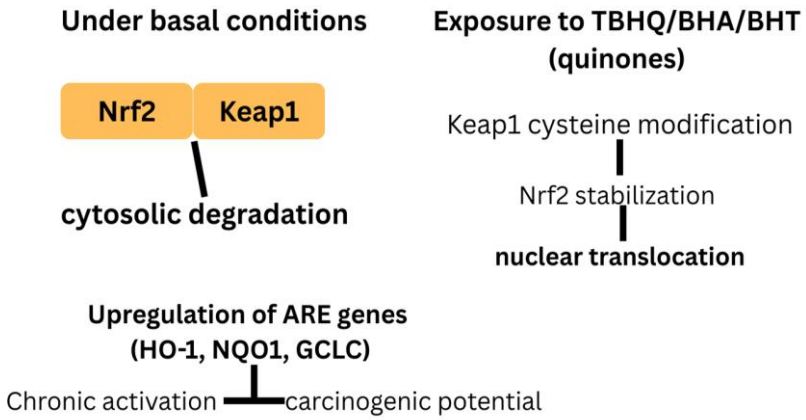


Figure 3: The triggering of the Nrf2 -Keap1 antioxidant response system by oxidative products of BHA, BHT and TBHQ, and subsequent cytoprotective and possible carcinogenic effects.

Continued oxidative stress and electrophilic injury by these substances trigger genetic and epigenetic changes. The BHT-QM is a direct alkylating agent and attaches to the

DNA, namely, the deoxyguanosine, which may cause base mispairing and mutations like GC, TA transversions (Gharavi and El-Kadi, 2005). The reactive oxygen species produced in TBHQ redox cycling, which is mainly superoxide and hydrogen peroxide, may overwhelm the endogenous antioxidant enzymes such as superoxide dismutase (SOD). Another recent research established that exposure to TBHQ caused significant decreases in the SOD activity, glutathione (GSH), as well as total antioxidant capacity and increases in malondialdehyde (MDA), which is a lipid peroxidation marker (Alahmadi et al., 2025).

Additionally, TBHQ dysregulates the homeostasis of thyroid hormones by altering T3/T4 levels and inhibiting thyroid hormone receptors. Its metabolite, TBBQ, causes oxidative DNA damage and blocks the process of DNA synthesis. Chronic modifications in DNA methylation, potentially linked to disease susceptibility, have also been observed in connection with exposure to TBHQ (Ren et al., 2025). Network toxicology analyses have also provided evidence of gene targets of TBHQ-induced toxicity, such as hepatotoxicity (TNF, IL6), nephrotoxicity (FOS), and neurotoxicity (GRIN2B), with in vivo evidence of cognitive impairment and histopathological alterations (Alahmadi et al., 2025). The immune system is an easily affected system. TBHQ hampers T-cell receptor activation, interferes with dendritic cell maturation and may alter immune balance, potentially increasing the susceptibility of the body to viral infections and allergies(Awali et al., 2025) (Boss, 2023). Recent research indicates an impact on gut microbiome; TBHQ has been observed to induce a pro-inflammatory response in the gut through the downregulation of tight junction proteins (Occludin, ZO-1) and to induce dysbiosis by adjusting the Firmicutes / Bacteroidetes ratio (Peng et al., 2009). The liver, which is the metabolic centre, is especially susceptible. At high doses, hepatotoxicity is caused by mitochondrial dysfunction, which is manifested by opening of the mitochondrial permeability transition pore (mPTP), collapse of mitochondrial membrane potential ($\Delta\Psi m$), and inhibition of electron transport chain complexes I and III. This causes the inhibition of the production of ATP and the release of cytochrome c, which initiates apoptosis (Ott et al., 2007). The BHT and TBHQ also cause renal toxicity through ferroptosis s(Angeli et al., 2014), which is an iron-dependent cell death that occurs via lipid peroxidation. Another risk is neurotoxicity as these substances block the growth of neurites and initiate neuroinflammation. The key principle is that the impact of these substances is dose-dependent: while small amounts consumed in the diet are generally considered safe, there is concern about their potential to accumulate – especially compounds like BHT in body fat. Consequently, very high or prolonged exposure can lead to a buildup of health issues, such as cancer and metabolic disorders (Kahl & Kappus, 1993).

Toxicokinetic (Absorption, Distribution, Metabolism, and Excretion)

Due to the common application of synthetic phenolic antioxidants (SPAs) in food, cosmetics, and plastics, there is a strong need to understand the toxicokinetics of these compounds to evaluate their safety (Mizobuchi et al., 2022). These substances are distinguished by high absorption rates, widely distributed into lipid-rich tissues and complicated metabolism leading to detoxification or metabolic activation. The ratio of these processes, as well as particular excretion rates, is going to define their bioaccumulation and further toxicological hazard. Gastrointestinal absorption of BHA, BHT and TBHQ is close to complete after oral ingestion, which is the main route of exposure among the general population (Additives et al., 2018). Their lipophilicity is inherent and helps in the diffusion of the intestinal epithelium passively (Zhang et al., 2023). Recent research involves the importance of membrane transporters; TBHQ may interact with the membrane transport system, transporter P-glycoprotein (P-gp), which can potentially restrict its overall absorption, and this is the reason it shows low apparent permeability in Caco-2 models in comparison with BHT (Bai et al., 2019).

Bile salts and dietary fats form mixed micelles, which is a very important solubilization process, and to a significant extent, increases bioaccessibility (McClements, 2018). It has been shown that with in vitro digestion, the BHT bioaccessible fraction is raised significantly more in the presence of fat (Mizobuchi et al., 2022). Although slower, dermal absorption is still a possible secondary route, especially to BHT in cosmetics. The in vitro human skin models demonstrated that the formulation vehicle affected the absorption profile, in which the oil-based formulations enhanced BHT penetration into the dermis and systemic circulation to a greater extent than water-based formulations. Inhalation exposure, which is mostly an occupational issue in food processing and plastics production, enables the effective exchange of alveolar gas and direct entry into the system without passing through hepatic metabolism (first-pass) (Oberdörster et al., 2002).

After the uptake, SPAs are quickly dispersed all over the body. Their physicochemical characteristics determine their tendency to get deposited in the fatty tissue (Additives & Food, 2012). Distribution is further influenced by protein binding. These compounds are bound to serum proteins, especially albumin and lipoproteins and form a reservoir of these compounds in the blood. The affinity of BHT to very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) in particular, because it can be transported to the tissues (Di Giulio et al., 2020). Translocation of such compounds to the secure location is also of toxicological significance. BHT and its metabolites placental transfer, and concentrations in the fetal liver are at lower level (Yang et al., 2025). Moreover, BHT metabolites were found in human breast milk which confirms lactational transfer (Zhang et al., 2020). It is worth noting that although parent compounds are typically excluded of the central nervous system, reactive endogenous products of TBHQ, including BHT-quinone methide (BHT-QM) and TBHQ-derived quinones, may enter the central nervous system through passive diffusion or by disrupting the integrity of the barrier by oxidative stress, which is a potential neurotoxic risk (Peluso, 2022).

Metabolism Hepatic metabolism regulates the ultimate biological destiny of SPAs, and trades detoxification with metabolic activation (Additives & Food, 2012). Phase I metabolism of BHT is a complex process that is primarily catalysed by the cytochrome P450 enzymes CYP2B6 and CYP2C19 (Gharavi et al., 2007). The oxidation produces BHT-OH, which is then further oxidized into BHT-CHO and BHT-COOH to be eliminated. But another route is the dehydration of BHT-OH to produce the highly reactive quinone methide (BHT-QM). BHT-QM is a soft electrophile that can easily form a covalent adduct with glutathione (GSH) and cellular proteins, both of which are directly related to hepatotoxicity and pneumotoxicity (Bolton et al., 2000). BHA is rapidly O-demethylated by CYP1A2 to TBHQ, and a direct metabolic connection exists between the two antioxidants (Additives & Food, 2011). TBHQ then undergoes a redox process to a semiquinone radical and then to tert-butylbenzoquinone (TBBQ). TBBQ converting into TBHQ by NQO1 produces superoxide anions, which sustain oxidative stress(Koh, 2009). However, this futile cycling of inactivated enzyme consumes NADPH and produces reactive oxygen species (ROS). Phase II conjugation is the major route of detoxification. UGTs and sulfation (SULTs) enzymes that form water-soluble conjugates, intended for urinary excretion, can become overloaded by high levels of TBHQ, and it is then forced into dangerous redox cycling reactions(Additives & Food, 2012). Equally, BHT-QM is highly reactive and has the potential to cause exhaustion of hepatic GSH stocks, rendering cells susceptible to the effects of oxidation (Gharavi et al., 2007). The major elimination pathway of water-soluble Phase II metabolites (glucuronides and sulfates). The rates of elimination vary between compounds. TBHQ and BHA are degraded comparatively faster, having short half-lives in animal models, respectively, due to their high rates of metabolism and lower lipid solubility (Xu et al., 2024). Conversely, the excretion of BHT is dose-related. Although it is efficient when

used at low doses, the half-life may be longer than 24 hours with high doses as adipose tissue accumulation exceeds the metabolic clearance (Ren et al., 2025). Systemic exposure of BHT is enhanced by enterohepatic circulation, since bile-excreted products can be returned to circulation by the action of enteric bacteria to deconjugate the metabolites for reabsorption into the circulatory system (Roberts et al., 2002). Faecal excretion explains the excretion of non-polar metabolites and non-absorbed content.

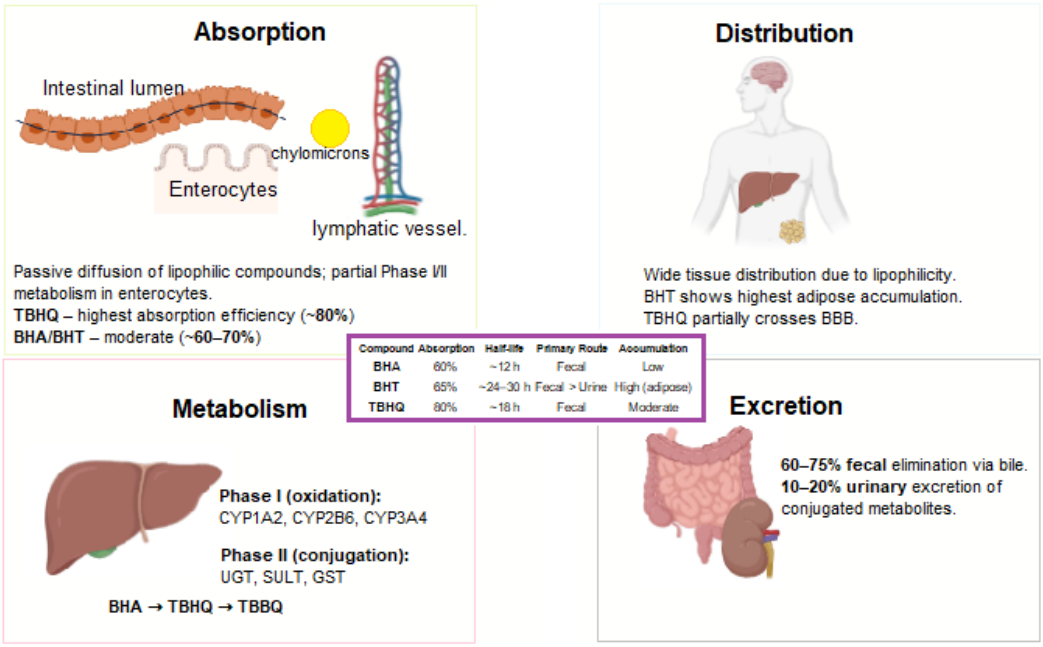


Figure 4: Global view of ADME of BHA, BHT, and TBHQ.

Each of the three compounds is readily absorbed and distributed to fatty tissues and subjected to Phase I oxidation and Phase II conjugation before excretion (Additives & Food, 2012). The metabolism of BHT produces electrophilic quinone methides, and BHA transforms to TBHQ that further produces redox-active semiquinone and benzoquinone derivatives(Bolton et al., 2000; Gharavi et al., 2007; Zhang et al., 2023). Evidence show potential for biomonitoring us that there are widespread exposure and bioaccumulation, especially in the case of BHT (Zhang et al., 2023). BHT-acid (BHT-COOH) and other metabolites have been found ubiquitously in urine, serum and human breast milk with high frequencies detection reported in some study groups (Mielech et al., 2021). The cumulative exposure of BHT is indicated by the presence of BHT residues in adipose tissue, hair, and nails (Zhang et al., 2023). Toxicokinetics of vulnerable groups are unique. Physiologically Based Pharmacokinetic (PBPK) models suggest that children ingest food additives at increased rates as a function of body weight and have immature metabolic capacities (Niehoff et al., 2022). As an example, CYP enzymes develop abnormalities at birth and become active during the age and may contribute to BHT clearance in children (Molina-Montes et al., 2021; Lin et al., 2024). During pregnancy, physiological changes may change the metabolism and the rate of clearance in the liver. Moreover, patients with underlying disorders (non-alcoholic fatty liver disease (NAFLD)) might have a compromised detoxification ability, which heightens the chances of bioaccumulation and the formation of toxic metabolites (Additives & Food, 2012). These factors should be included in recent risk assessment methods to provide sufficient safeguards to vulnerable subpopulations.

Exposure and Biomonitoring.

The exposure of human beings to BHA, BHT and TBHQ is widespread, and it can happen in various channels because of the wide use of these additives in the food

sector, consumer products, and in the industrial production process. The general population mainly gets exposed to these preservatives because manufacturers add them directly to processed foods, which need protection against oxidative rancidity (Additives & Food, 2012). Some of the most important sources of dietary exposure are edible oils, margarine, cereals, baked goods, confectionery, dehydrated potatoes, chewing gum, and fried foods like instant noodles and crackers (Oliveira et al., 2025). The additive concentrations are typically within regulatory limits, although this varies depending on the particular compound and food matrix(Additives & Food, 2012). There are also regional differences in usage patterns; an example is that TBHQ is widely used in frying oils in the United States and Asia, and BHT is widely used in cereals and snacks, albeit its usage is decreasing in the European Union due to increased regulatory control (Oliveira et al., 2025). There are always high-risk food groups that have high levels of additives, such as instant noodles (seasoning oil packets, in particular), microwave popcorn, processed meats, and frying oils used in commercial food service over and over again. Therefore, the exposure of high-consumption subpopulations in Asia to TBHQ has been observed to have the potential to approach or exceed the Acceptable Daily Intake (ADI) in high consumers (Liu & Mabury, 2020).

Another important but frequently overlooked secondary diet route is the excretion of antioxidants by food contact materials. BHA, BHT, and TBHQ are part of plastics (e.g., polyethene, polypropylene), adhesives and laminates in packaging to stabilize polymers (Nilsen-Nygaard et al., 2021). These compounds may be transferred to food, and the degree of migration depends on the duration of contact, temperature, and lipid levels in food. Although the typical migration is between 0.05 and 5 mg/kg, high-temperature conditions or long-term storage of oil (as in the case of bottled oils or ready-to-eat meals) may increase under high temperature or prolonged storage (Nilsen-Nygaard et al., 2021). This is of special concern to the health of babies, where the migration of baby food pouch liners, formula containers, and plastic utensils can lead to disproportionately high exposures in sensitive developmental stages (Dai et al., 2025).

The other exposure routes do not include dietary exposures, but they also play a role in the body burden. One of the significant sources of BHT, which is a stabilizer widely used in lipsticks, moisturizers, sunscreens, and deodorants, is through dermal absorption into the body. Dermal absorption is rather low but measurable; the regular use of several products leads to a stable internal dose, which is estimated to be low but continuous exposure levels in regular users (Api et al., 2020) (Hoang & Park, 2024). One of the emerging issues is environmental exposure; the BHT and its transformation products are often found in surface waters, wastewater effluent and indoor dust, reported in μg/g, which is a particular threat to young children by non-dietary ingestion and hand-to-mouth contact (Y. Wang et al., 2025). Moreover, food processing and packaging manufacturing, as well as cosmetic production, potentially exposure occurs through combined inhalation and dermal routes, resulting in internal exposure levels that are much higher than those of the general population (Chung et al., 2021).

The internal exposure is also very high, as human biomonitoring studies reveal that the compounds and their metabolites are found in different biological matrices. The most commonly monitored is the presence of urinary biomarkers, where the detection of the metabolites of BHT (BHT-COOH, BHT-OH) and TBHQ conjugates (sulfates, glucuronides) is observed in a significant proportion of the population, in the US, Europe, and Asia, which suggests widespread and persistent exposure (Veyrand et al., 2017; Xu et al., 2022). The research results show that bioaccumulation and maternal transfer to the offspring should be considered the main threat. BHT metabolites have been found in human serum, fatty tissue, and breast milk multiple times, which confirms the long-term retention of BHT in the body and the exposure of the nursing

newborn to it The BHT metabolites in keratinized tissues, which include hair and fingernails, serve as a permanent indicator of exposure, and a 2022 cohort study found BHT-COOH in more than 90 percent of hair samples that were examined (Xu et al., 2022).

Primary human exposure routes to BHA, BHT, and TBHQ. Exposure is mostly due to dietary sources and is complemented by movement of food-contact materials, personal care products, occupational settings and environmental matrices (Api et al., 2020; Ji et al., 2023). Vulnerable Populations and Cumulative Risk Analysis of exposure Data reveal that certain subpopulations are at an increased risk. Infants and young children are high exposure per body weight than adults. This difference is fueled by increased food consumption in comparison to body mass and incomplete metabolic capacity (Molina-Montes et al., 2021). The pregnant women are also a vulnerable group of individuals because of the physiological changes that change toxicokinetics and transplacental transfer potential due to the presence of BHT metabolites in umbilical cord blood (Veyrand et al., 2013). Moreover, teens and adults with high-fat diets like processed or fried foods may approach or exceed the ADI of TBHQ (Liu & Mabury, 2020; Molina-Montes et al., 2021). The present risk assessments normally consider these compounds separately. But real-life exposure is combined across many sources (diet, packaging, cosmetics) and co-exposure to many SPAs. Both BHT and TBHQ cause oxidative stress through similar pathways which may have additive or synergistic effects. May not fully account for cumulative effects (Bolton et al., 1990; Peluso et al., 2025).

Table 2. BHA, BHT and TBHQ Estimated Daily Intake (EDI) Ranges and Important Exposure Sources.

Compound	**General Population EDI (mg/kg bw/day)**	**High-Consumer EDI (mg/kg bw/day)**	**Key Dietary Sources**	**Key Non-Dietary Sources**
BHA	0.01 – 0.1	0.1 – 0.3	Cereals, baked goods, processed meats, chewing gum	Packaging migration, limited cosmetic use
BHT	0.02 – 0.16	0.2 – 0.6	Snack foods, margarine, cereals, edible oils	**Cosmetics (lipsticks, creams),** packaging migration, indoor dust
TBHQ	0.02 – 0.12	0.2 – 0.8	**Frying oils, instant noodles, crackers,** fish oil supplements	Packaging migration, occupational inhalation in food service

Important Uncertainties and Data Gaps Although there is already data available, there are still major uncertainties in exposure assessment. They are the lack of particular biomonitoring information on BHA metabolites as well as the lack of description of

cumulative exposure during multiple pathways (dietary, dermal, inhalation) that occur concomitantly. Moreover, cumulative risk assessment models have not been developed to consider the cumulative toxicological effects of co-exposure to BHA, BHT, and TBHQ, especially by common pro-oxidant act (Additives et al., 2018; Liu & Mabury, 2020). Also, the risk of environmental re-exposure via contaminated water and dust is limited data available, and it could lead to baseline body burdens. These gaps need to be addressed towards an accurate and protective public health risk assessment.

Toxicity Profiles of BHA, BHT and TBHQ.

The toxicology of BHA, BHT, and TBHQ is characterized by a paradoxical situation: they are the strong antioxidants in food matrices, but at the same time, they can cause serious adverse effects in biological systems, and their active metabolites can be the primary causes of these effects (Gharavi & El-Kadi, 2005; Liu & Mabury, 2020). Metabolic activation to pro-oxidant and electrophilic species is a major factor in the toxicity of these synthetic phenolic antioxidants. The process leads to cellular imbalances which include oxidative stress and genotoxicity and endocrine disruption and specific organ damage (Gharavi & El-Kadi, 2005; Z. Wang et al., 2025). The parent compounds do not dictate the toxic potential; the toxicity is instead regulated by the dosage, length of exposure and metabolic competence of the individual. As a result, children, pregnant women, and people with underlying metabolic issues might be at a greater risk (Liu & Mabury, 2020).

Toxicity in SPA is mainly due to antioxidant to pro-oxidant conversion. The compounds produce oxidative stress when they reach elevated levels or undergo metabolic activation. TBHQ can act as a strong pro-oxidant under certain condition, which undergoes redox cycling between hydroquinone and quinone redox states (tert-butylbenzoquinone, TBBQ). The cycle continuously produces radicals of superoxide anions at the expense of cellular reducing agents like NADPH (Tamarin et al., 2026). BHT is broken down to an electrophilic quinone methide (BHT-QM) by cytochrome P450 enzymes. Being a soft electrophile, BHT-QM can easily react to nucleophilic sites on glutathione (GSH) and cellular proteins which causes a significant decline in antioxidant capacity and affects protein functionality (Bolton & Thompson, 2009). BHA and TBHQ both share metabolic mechanism and per oxidation pathway (Additives & Food, 2011). Important early targets are mitochondria. TBHQ and BHT metabolites inhibit complexes I and III of the electron transport chain causing mitochondrial membrane depolarization, inhibition of ATP production, and discharge of pro-apoptotic factors including cytochrome c. This pathway eventually leads to hepatic and neuronal cell apoptosis at low concentrations in experimental system (Ren et al., 2025).

Genotoxicity, Epigenetic Changes and Carcinogenic Risks Long-term oxidative stress and electrophilic assault using the SPA metabolites cause serious genetic and epigenetic damage. The TBHQ and BHT-QM quinones lead to oxidative DNA damage, including the formation of an oxidative promutagenic lesion, 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), and DNA strand breakage (Peluso, 2022; Rao & Zheng, 2025). Moreover, BHT-QM is a direct alkylating agent, which produces DNA adducts resulting in base mispairing and chromosome abnormalities such as the formation of micronuclei (Gharavi & El-Kadi, 2005). The compounds create epigenetic modifications together with their direct genotoxic effects. TBHQ and BHT have been found to alter global DNA methylation and histone acetylation of neuronal and hepatic cells, which may lead to long-term alterations in gene expression of a stress response and cell cycle regulation (Rao & Zheng, 2025) Xu et al., 2020). It is based on these mechanisms that the carcinogenicity concerns are founded. BHA is considered as Group 2B (possibly carcinogenic to humans) by the International Agency on Research on Cancer (IARC) due to evidence of forestomach tumors in

rodents, which is probably due to chronic cytotoxicity and compensatory cell proliferation (Additives & Food, 2011). Although BHT data are controversial, TBHQ is not a direct carcinogen but can be a tumor promoter by creating a pro-inflammatory pro-oxidant microenvironment that favors survival of initiated cells (Additives & Food, 2011; Peluso, 2022).

Endocrine and Immune System Disruption SPAs are endocrine-disrupting chemicals (EDCs), which disrupt hormone homeostasis. BHT is a weak estrogenic agonist and an androgen agonist, which attaches to the estrogen receptor alpha and the androgen receptor (AR), and interferes with the sex hormone signaling (Kumar et al., 2019). TBHQ interferes with homeostasis of thyroid hormones by reducing the levels of circulating T3 and T4 and blocking the effect of thyroid hormone activation enzymes (S. Wang et al., 2025). BHA and BHT also disrupt steroidogenesis, modulate the production of progesterone and testosterone in reproductive and adrenal tissues (Gao et al., 2022). Consistent with this, animal studies on cobalt-based nanomaterials reported parallel modulation of sex hormones, thyroid function, and metabolic parameters (Umar et al., 2024b; Umar et al., 2025a), reinforcing the broader relevance of metal-induced endocrine disruption across different toxicant classes. The immune system serves as a primary target which shows high sensitivity to the effects. TBHQ has been reported strong immunomodulatory effects. It silences T-cell receptor signalling, suppresses crucial cytokines like IL-2 and IFN-g, impairs the development of dendritic cells and biases the immune response towards a Th2-dominated phenotype. Such a change may increase the risks of viral infections and sensitization to allergies (Liu & Mabury, 2020; Whisel, 2025)These immunotoxic effects are particularly alarming because they are found at exposure levels that are pertinent to human consumption.

Organ-Specific Toxicity and Emerging Targets The cumulative damage to cells is in the form of organ-specific toxicity. Liver being the main site of metabolism is very vulnerable. The three SPAs cause hepatotoxicity in the form of increased liver enzymes, microvesicular steatosis (through PPARalpha and SREBP-1c interference) and inflammatory infiltration (Kumar et al., 2019; H.-J. Zhao et al., 2020). Parallel in vivo studies on metal-based nanomaterials have similarly demonstrated dose-dependent liver enzyme elevations and hepatic inflammatory infiltration (Umar et al., 2024a; Aslam et al., 2025b), corroborating the organ-level toxicity patterns observed with SPAs. It also raises the risk of the nervous system, with quinone metabolites entering the blood-brain barrier and impairing neurite outgrowth, interfering with the functioning of synaptic mitochondria and inducing apoptosis. This neurotoxicity is associated with negative effects on rodent models, such as worse locomotor activity and worsened memory (Savin et al., 2022; S. Wang et al., 2025). Another issue is nephrotoxicity, whereby the BHT and TBHQ analogues are found in the renal cortex, leading to oxidative stress of proximal tubule cells and increased serum creatinine and blood urea nitrogen (BUN) (Liu & Mabury, 2020). These toxicological endpoints mirror findings in rodent models exposed to copper oxide and cobalt-based nanoparticles, where significant alterations in hematological parameters and renal biochemical markers were documented (Abbas et al., 2025; Umar et al., 2026a), suggesting shared organ-level susceptibility pathways. The problem of gut toxicity has become an emerging issue in the medical field. TBHQ affects the intestinal barrier by downregulating tight junction proteins (H.-J. Zhao et al., 2020).

Cumulative Risk and Vulnerable Populations Current toxicological evaluations usually assess chemicals separately, but in reality, there is exposure of chemicals as combinations. The study shows that multiple chemical exposure creates higher health risks than single chemical tests indicate (Bolton & Thompson, 2009). The disproportionate risks are experienced by vulnerable populations. Exposure to children is greater as compared to body weight and immature metabolism. Women who are pregnant are capable of transmitting the metabolites to the developing fetus

through the placenta since the metabolites of BHT are detected in the cord blood (Mielech et al., 2021). Mechanistic, animal, and biomonitoring data, collectively, suggest that standard dietary exposure is likely to be low, but bioaccumulation (especially BHT) and cumulative effects could be present, and a new risk assessment approach should be considered.

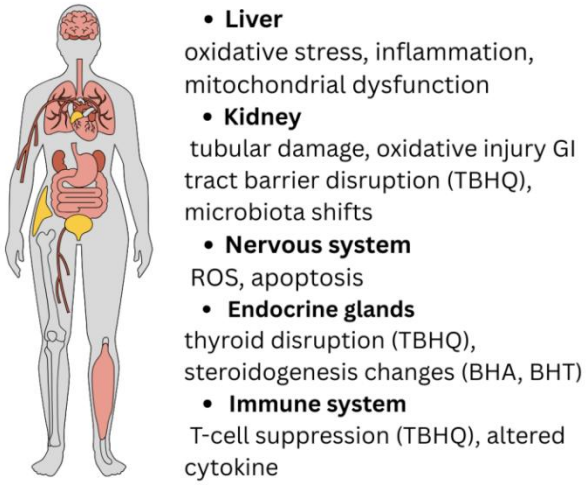


Figure 5 Showing liver, kidney, gastrointestinal tract, nervous system, endocrine organs and immune system effects.

Table: 3 Summary of organ-specific toxicity of BHA, BHT and TBHQ

Toxicological Endpoint	**BHA**	**BHT**	**TBHQ**	**Key Supporting Evidence**
Primary Mechanism	Metabolic conversion to TBHQ	Quinone Methide (BHT-QM) formation	Redox Cycling & Quinone formation	(Bolton & Thompson, 2009) (Additives & Food, 2011)
Oxidative Stress Potential	Moderate	High	**Very High**	(Gharavi & El-Kadi, 2005) (S. Wang et al., 2025)
Genotoxicity	Weak–Moderate	Moderate	**Strong**	(Peluso, 2022; H.-J. Zhao et al., 2020)
Carcinogenicity	IARC Group 2B	Not Classified	Not Classified (Tumor promoter)	(Additives & Food, 2011)
Endocrine Disruption	Alters steroidogenesis	Weak estrogenic/anti-androgenic	**Thyroid disruption**	(Gao et al., 2022; S. Wang et al., 2025)
Immunotoxicity	Limited / Mixed	Moderate	**Strong**	(Mielech et al., 2021) (S. Wang et al., 2025)
Neurotoxicity	Moderate	Moderate	**High**	(Savin et al., 2022) (Peluso,

Toxicological Endpoint	BHA	BHT	TBHQ	Key Supporting Evidence
				2022) (H.-J. Zhao et al., 2020)
Key Organ Toxicity	Forestomach , Liver	Liver, Kidney	Liver, GI Tract	(S. Wang et al., 2025; H.-J. Zhao et al., 2020)

Risk Assessment and regulatory environment.

The international control of BHA, BHT and TBHQ is varies significantly, due to the differences in interpretation of toxicology and the precautionary principle. Although these synthetic phenolic antioxidants (SPAs) are still allowed in most places, there is an apparent discrepancy between traditionally based regulations and more evidence-based, careful approaches. This deviation is prompted by recent discoveries about the endocrine disruption, immunotoxicity, and cumulative exposure, which were not adequately taken into consideration during the safety evaluation at the first stage (Additives & Food, 2016) FDA, 2022).

Global Regulatory Frameworks The basis of the existing regulations is historical approvals decades old, based on the toxicological standards which focused more on overt toxicity and carcinogenicity rather than on the more subtle mechanistic effects. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has set early Acceptable Daily Intakes (ADIs) of 0–0.5, 0, and 0.7 mg/kg bw/day of BHA, BHT, and TBHQ, respectively, on the basis of rodent bioassay No-Observed-Adverse-Effect-Levels (NOA The Codex Alimentarius Commission has since adopted these standards, which are regarded as the standard of many developing countries (Session, 2007). Greater regional inequalities exist. The United States, through the FDA, has a rather permissive position concerning the so-called Generally Recognized as Safe (GRAS) category that permits as much as 0.02 percent of the fat or oil composition (Additives et al., 2022). It has been criticized as basing on industry-funded data and not having mandatory re-evaluation schedules (Pomeranz et al., 2024). The European Union, led by the European Food Safety Authority (EFSA) on the other hand has assumed a precautionary stance. BHA and BHT are not allowed in infants and young children food, and EFSA has tightened ADIs (Additives & Food, 2016). Moreover, the EU has realized the importance of non-dietary routes, the Specified Migration Limits (SML) of packaging materials are introduced, and a safe limit of 0.5 mg/kg BHA is established (EU No. 10/2011). Japan has also implemented strict prohibitions on BHA in baby food, and other large economies such as China and Australia/New Zealand are moving towards stricter regulations or towards natural substitutes because of consumer demand (Duan et al., 2025; Magnuson et al., 2013).

Issues in the Modern Risk Assessment The existing risk assessment systems have an inherent limitation in their application in relation to SPAs. The major drawback is the use of old toxicological premises. Normal ADIs are based on research not focused on contemporary endpoints like low-dose endocrine effect or developmental immunotoxicity. As an example, anti-androgenic effects of BHT and the thyroid-disturbing qualities of TBHQ were not factored into the initial risk evaluations (Paramasivam et al., 2024; Zhang et al., 2025). Moreover, universally, regulations do not consider realistic exposure scenarios. A combination of these antioxidants available to man concurrently and their actions may be synergistic. BHA and TBHQ share similar metabolic pathway which is effective in enhancing the burden of quinones in the body, whereas BHT and TBHQ may have an additive effect on reducing the glutathione stores (Bolton et al., 2000; Paramasivam et al., 2024). This

cumulative exposure, which is reinforced by cosmetics (e.g., BHT in lipsticks) and environmental routes (e.g., indoor dust) is not included in regular dietary risk evaluations (Ji et al., 2023). The situation in biomonitoring indicates the inefficiency of the existing models. The presence of BHT metabolites in hair samples and TBHQ conjugates in urine of adolescents indicate that the internal exposure is more significant than anticipated by dietary models. Probabilistic and Physiologically Based Pharmacokinetic (PBPK) modeling suggests that children and high consumers often approach or exceed the ADI, and there is a very limited safety margin (Ji et al., 2023).

Future Perspectives and Research Recommendation To close the gap between present-day regulations and contemporary science, a paradigm shift in the risk assessment and research priorities is necessary.

The research of future studies should implement omics technologies and high-content screening methods to establish Adverse Outcome Pathways AOPs which include their dose-response relationships that affect endocrine and immune system functions based on (Ji et al., 2023).

Mixture Toxicity Assessment: Studies should no longer be limited to individual-chemical analyses. It may be beneficial to create of TBHQ-equivalency approches to measure the cumulative burden of antioxidants that are metabolically related (Paramasivam et al., 2024).

Advanced Exposure Science: Biomonitoring programs are strongly recommmended on a large scale to monitor exposure in at-risk populations (pregnant women, infants) and to measure non-dietary exposures such as dermal absorption of cosmetics (Ji et al., 2023; Shahidi & Zhong, 2010b).

Protection of Vulnerable Populations: PBPK modeling should be considered in risk assessments to model internal doses at various life stages beyond simple safety factors to define health-based guidance values that are specific to children (Paramasivam et al., 2024).

Global Harmonization and Alternatives: The trade complexities and inequality in protection between the EU and US arise because of regulatory divergence. At the same time, the development of safer and natural alternatives to this should be hastened (e.g., natural or alternate antioxidants; nanoencapsulated plant extracts) to satisfy consumer needs in clean-label preservation (Kamal-Eldin & Pokorny, 2020).

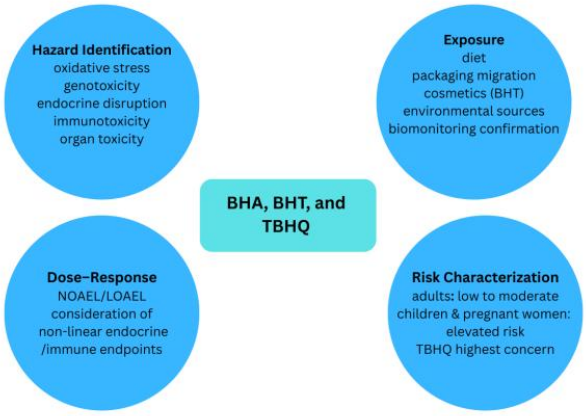


Figure 6. BHA, BHT, and TBHQ: A complex risk assessment model that includes the combination of hazard identification, dose-response analysis, and exposure analysis with the current biomonitoring information.

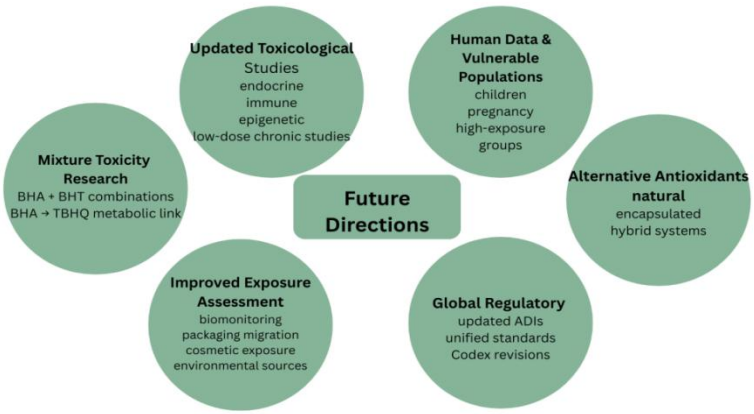


Figure 7. Research priorities in the future, such as mechanistic toxicology updates, mixture toxicity assessment, and designing safer antioxidant alternatives.

Conclusion

BHA, BHT and TBHQ continue to play a significant role in the food, pharmaceutical, and cosmetic sectors due to their stability, effectiveness, and affordability. Nevertheless, their biological effect is much greater than their main role as free radical scavengers. There is growing evidence that these compounds are associated with oxidative stress and endocrine disruption, immunomodulation, genotoxicity, and organ-specific toxicity at lower levels of exposure than those used in historical safety evaluations (Gharavi and El-Kadi, 2005; Eskandani et al., 2014; Ren et al., 2025). Although existing dietary assessments indicate that mean intakes in most cases are below recommended ADIs, biomonitoring results reveal that cumulative internal exposure is not as low as that predicted by regulatory modeling. This is especially noticeable in individuals of young age and adolescents, as well as in those who consume fried and packaged foods in large amounts (Yang et al., 2022; Veyrand et al., 2013). The metabolic interconversion (e.g., BHA to TBHQ), long-term sources of exposure in the environment, and the widespread nature of such antioxidants in various consumer products make the issue of real-world exposure even more complicated.

The existing risk assessment systems of BHA, BHT, and TBHQ are still heavily rooted in old datasets that do not take into consideration the contemporary mechanistic toxicology, mixture effects, endocrine endpoints, and human biomonitoring data. This dependency on past data prevents the assessment of whether the current safety levels are adequate for all subgroups in the population. This review indicates that more rigid exposure limits to susceptible groups, such as children, pregnant women, and those with pre-existing metabolic sensitivities, should be considered. At the same time, to minimize the use of synthetic additives, regulatory bodies and the food industry are turning to safer options, including natural antioxidants and advanced encapsulation technologies (Shahidi and Ho, 2021; Wrona et al., 2020). Further investment into researching and proofing these alternatives must be made to ensure reduced consumer exposure without sacrificing the food quality or shelf life.

In the future, risk assessment frameworks must be developed to embrace the latest toxicological approaches, the holistic biomonitoring, the cumulative mixture modeling, and the vulnerability of life stages. It will be essential to harmonize the international regulatory standards and update Acceptable Daily Intakes (ADIs) in accordance with the prevailing science and knowledge in order to provide a coherent and protective attitude towards the health of the population. To sum it up, although BHA, BHT, and TBHQ are still effective antioxidants, they should be reconsidered in modern times, becoming more data-oriented and ensuring their safe use in the ever-changing environment of food and consumer goods.

Reference:

Additives, E. P. o., Feed, P. o. S. u. i. A., Bampidis, V., Azimonti, G., Bastos, M. d. L., Christensen, H., Dusemund, B., Fašmon Durjava, M., Kouba, M., López-Alonso, M., & López Puente, S. (2022). Safety and efficacy of a feed additive consisting of butylated hydroxytoluene (BHT) for all animal species (Lanxess Deutschland GmbH). *EFSA Journal*, *20*(5), e07286.

Additives, E. P. o., Feed, P. o. S. u. i. A., Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. d. L., Bories, G., Chesson, A., Cocconcelli, P. S., & Flachowsky, G. (2018). Safety and efficacy of butylated hydroxyanisole (BHA) as a feed additive for all animal species. *EFSA Journal*, *16*(3), e05215.

Additives, E. P. o. F., & Food, N. S. a. t. (2011). Scientific Opinion on the re-evaluation of butylated hydroxyanisole–BHA (E 320) as a food additive. *EFSA Journal*, *9*(10), 2392.

Additives, E. P. o. F., & Food, N. S. a. t. (2012). Scientific Opinion on the re-evaluation of butylated hydroxytoluene BHT (E 321) as a food additive. *EFSA Journal*, *10*(3), 2588.

Additives, E. P. o. F., & Food, N. S. a. t. (2016). Statement on the refined exposure assessment of tertiary-butyl hydroquinone (E 319). *EFSA Journal*, *14*(1), 4363.

Alahmadi, S., Alanazi, M. M., Alasmari, F., Al-Qahtani, W. S., & Albasher, G. (2025). The Efficiency of Chitosan Against Tert Butylhydroquinone (TBHQ)-induced neurobehavioral changes and toxicity effects in male rats. *Frontiers in Bioscience-Landmark*, *30*(1), 26871.

Almuraee, A. A. (2025). Nano-Formulated Herbal Bioactives in Animal-Based Functional Foods: A Nutritional Approach to Enhancing Bioavailability and Health Benefits. *Applied Food Research*, 101587.

Alnuqaydan, A. M. (2024). The dark side of beauty: an in-depth analysis of the health hazards and toxicological impact of synthetic cosmetics and personal care products. *Frontiers in public health*, *12*, 1439027.

Angeli, J. P. F., Proneth, B., Hammond, V. J., Tyurina, Y. Y., Tyurin, V. A., ODonnell, V. B., Kagan, V. E., & Conrad, M. (2014). Inactivation of the Ferroptosis Regulator Gpx4 Triggers Acute Renal Failure in a Therapeutically Relevant Mechanism: 170. *Free Radical Biology and Medicine*, *76*, S77-S78.

Api, A. M., Belsito, D., Biserta, S., Botelho, D., Bruze, M., Burton, G., Buschmann, J., Cancellieri, M., Dagli, M., & Date, M. (2020). RIFM fragrance ingredient safety assessment, citral, CAS Registry Number 5392-40-5. *Food Chem. Toxicol*, *141*(Suppl 1), 111339.

Aslam, M. W., Umar, A., Khan, M. S., Wajid, M., Sabri, S., & Khan, M. U. (2025). Sub-chronic toxicity of chemically synthesized CuO-NPs in albino mice. *Biomarkers*, *30*(7), 486-502.

Awali, S., Jin, Y., Duriancik, D. M., & Rockwell, C. E. (2025). The Nrf2 activator tBHQ inhibits dendritic cell maturation and activation in response to bacterial and viral stimuli. *Toxicology in Vitro*, 106169.

Ayala-Fuentes, J. C., & Chavez-Santoscoy, R. A. (2021). Nanotechnology as a Key to Enhance the Benefits and Improve the Bioavailability of Flavonoids in the Food Industry. *Foods*, *10*(11), 2701.

Bai, J., Zhao, S., Fan, X., Chen, Y., Zou, X., Hu, M., Wang, B., Jin, J., Wang, X., & Hu, J. (2019). Inhibitory effects of flavonoids on P-glycoprotein in vitro and in vivo: Food/herb-drug interactions and structure–activity relationships. *Toxicology and applied pharmacology*, *369*, 49-59.

Barbouti, A., Varvarousis, D. N., & Kanavaros, P. (2025). The role of oxidative stress-induced senescence in the pathogenesis of preeclampsia. *Antioxidants*, *14*(5), 529.

Baumann, S. (2020). Shelf life analysis of cereal products processed with and without BHT.

Beynen, A. C. TBHQ in dog food.

Bhattarai, B. (2019). *Effect of Different Synthetic Antioxidants in the Stability of Palm Oil on Deep Fat Frying of Instant Noodles*

Bolton, J. L., Sevestre, H., Ibe, B. O., & Thompson, J. A. (1990). Formation and reactivity of alternative quinone methides from butylated hydroxytoluene: possible explanation for species-specific pneumotoxicity. *Chemical research in toxicology*, *3*(1), 65-70.

Bolton, J. L., & Thompson, J. A. (2009). Formation and reactions of xenobiotic quinone methides in biology. *Quinone Methides*, 329-356.

Bolton, J. L., Trush, M. A., Penning, T. M., Dryhurst, G., & Monks, T. J. (2000). Role of quinones in toxicology. *Chemical research in toxicology*, *13*(3), 135-160.

Boss, A. P. (2023). *The Effects of Tert-Butylhydroquinone on the Murine Natural Killer Cell Activation, Effector Function, and Primary Response to Influenza*. Michigan State University.

Bouayed, J., & Bohn, T. (2010). Exogenous antioxidants—Double-edged swords in cellular redox state: Health beneficial effects at physiologic doses versus deleterious effects at high doses. *Oxidative medicine and cellular longevity*, *3*(4), 228-237.

Chib, A., Gupta, N., Bhat, A., Anjum, N., & Yadav, G. (2020). Role of antioxidants in food. *Int. J. Chem. Stud*, *8*, 2354-2361.

Chung, M. K., Rappaport, S. M., Wheelock, C. E., Nguyen, V. K., van der Meer, T. P., Miller, G. W., Vermeulen, R., & Patel, C. J. (2021). Utilizing a biology-driven approach to map the exposome in health and disease: an essential investment to drive the next generation of environmental discovery. *Environmental Health Perspectives*, *129*(8), 085001.

Dai, S., Liang, M., Cheng, H., Yu, C., Li, W., Lai, F., Ma, L., & Liu, X. (2024). Thermal decomposition characteristics of BHT and its peroxide (BHTOOH). *BMC chemistry*, *18*(1), 87.

Dai, W., Xiong, H., Sun, W., Zhou, C., Tan, C.-P., Li, B., & Xu, Y.-J. (2025). Emulsion Gels in Food Systems: Advances, Oxidative Stability Challenges, and Mitigation. *Food Reviews International*, *41*(9), 3345-3366.

de la Vega, M. R., Chapman, E., & Zhang, D. D. (2018). NRF2 and the Hallmarks of Cancer. *Cancer cell*, *34*(1), 21-43.

de Oliveira, L. P., Rocha, D. P., de Araujo, W. R., Muñoz, R. A. A., Paixão, T. R. L. C., & Salles, M. O. (2018). Forensics in hand: new trends in forensic devices (2013–2017). *Analytical methods*, *10*(43), 5135-5163.

Di Giulio, R., Benson, W., Sanders, B., & Van Veld, P. (2020). Biochemical mechanisms: metabolism, adaptation, and toxicity. In *Fundamentals of aquatic toxicology* (pp. 523-561). CRC Press.

Duan, M., Zhu, Z., Pi, H., Chen, J., Cai, J., & Wu, Y. (2025). Mechanistic Insights and Analytical Advances in Food Antioxidants: A comprehensive review of molecular pathways, detection technologies, and nutritional applications. *Antioxidants*, *14*(4), 438.

Fouda, S., Vennikandam, M. M., Pappachan, J. M., & Fernandez, C. J. (2022). Pregnancy and metabolic-associated fatty liver disease: a clinical update. *Journal of Clinical and Translational Hepatology*, *10*(5), 947.

Galanakis, C. M. (2022). *The age of clean label foods*. Springer.

Gao, X., Wang, X., Wang, X., Fang, Y., Cao, S., Huang, B., Chen, H., Xing, R., & Liu, B. (2022). Toxicity in Takifugu rubripes exposed to acute ammonia: Effects on immune responses, brain neurotransmitter levels, and thyroid endocrine hormones. *Ecotoxicology and environmental safety*, *244*, 114050.

García, C. D., & Ortiz, P. I. (2000). BHA and TBHQ quantification in cosmetic samples. *Electroanalysis: An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis*, *12*(13), 1074-1076.

Gharavi, N., & El-Kadi, A. O. (2005). tert-Butylhydroquinone is a novel aryl hydrocarbon receptor ligand. *Drug metabolism and disposition*, *33*(3), 365-372.

Gharavi, N., Haggarty, S., & S El-Kadi, A. O. (2007). Chemoprotective and carcinogenic effects of tert-butylhydroquinone and its metabolites. *Current drug metabolism*, *8*(1), 1-7.

Hoang, N. M., & Park, K. (2024). Applications of tert-butyl-phenolic antioxidants in consumer products and their potential toxicities in humans. *Toxics*, *12*(12), 869.

Inoue, T., Ikeda, D., Sugiyama, M., Suenaga, A., Kawashima, M., Kondo, E., & Umemura, T. (2025). Revised guidelines for the risk assessment of food additives in Japan. *Food Safety*, *13*(1), 7-14.

Ji, X., Liang, J., Wang, Y., Liu, X., Li, Y., Liu, Q., & Liu, R. (2023). Synthetic antioxidants as contaminants of emerging concern in indoor environments: knowns and unknowns. *Environmental Science & Technology*, *57*(51), 21550-21557.

Kahl, R., & Kappus, H. (1993). Toxicology of the synthetic antioxidants BHA and BHT in comparison with the natural antioxidant vitamin E. *Zeitschrift fur Lebensmittel-untersuchung und-forschung*, *196*(4), 329-338.

Kamal-Eldin, A., & Pokorny, J. (2020). Antioxidants in Food Preservation. In *Handbook of Food Preservation* (pp. 299-322). CRC Press.

Karamac, M., & Amarowicz, R. (1997). Antioxidant activity of BHA, BHT and TBHQ examined with Miller's test. *Grasas y Aceites*, *48*(2), 83-86.

Khezerlou, A., pouya Akhlaghi, A., Alizadeh, A. M., Dehghan, P., & Maleki, P. (2022). Alarming impact of the excessive use of tert-butylhydroquinone in food products: A narrative review. *Toxicology reports*, *9*, 1066-1075.

Koh, G. Y. (2009). *Preparation of the Chinese sweet leaf tea extract and its anti-obesity effect in rodents*. Louisiana State University and Agricultural & Mechanical College.

Kumar, N., Singh, A., Sharma, D. K., & Kishore, K. (2019). Toxicity of food additives. In *Food safety and human health* (pp. 67-98). Elsevier.

Lanigan, R. S., & Yamarik, T. A. (2002). Final report on the safety assessment of BHT (1). *International journal of toxicology*, *21*, 19-94.

Liu, R., & Mabury, S. A. (2020). Synthetic phenolic antioxidants: A review of environmental occurrence, fate, human exposure, and toxicity. *Environmental Science & Technology*, *54*(19), 11706-11719.

Liu, X., Zheng, Z., & Liu, Y. (2025). Lipophilic antioxidants in edible oils: Mechanisms, applications and interactions. *Food Research International*, *200*, 115423.

Magnuson, B., Munro, I., Abbot, P., Baldwin, N., Lopez-Garcia, R., Ly, K., McGirr, L., Roberts, A., & Socolovsky, S. (2013). Review of the regulation and safety assessment of food substances in various countries and jurisdictions. *Food Additives & Contaminants: Part A*, *30*(7), 1147-1220.

Maziero, G. C., Baunwart, C., & Toledo, M. C. F. (2001). Estimates of the theoretical maximum daily intake of phenolic antioxidants BHA, BHT and TBHQ in Brazil. *Food Additives & Contaminants*, *18*(5), 365-373.

McClements, D. J. (2018). Enhanced delivery of lipophilic bioactives using emulsions: a review of major factors affecting vitamin, nutraceutical, and lipid bioaccessibility. *Food & function*, *9*(1), 22-41.

Meier, B. W., Gomez, J. D., Kirichenko, O. V., & Thompson, J. A. (2007). Mechanistic basis for inflammation and tumor promotion in lungs of BHT-

treated mice: electrophilic metabolites alkylate and inactivate antioxidant enzymes. *Chemical research in toxicology*, *20*(2), 199.

Mielech, A., Puścion-Jakubik, A., & Socha, K. (2021). Assessment of the risk of contamination of food for infants and toddlers. *Nutrients*, *13*(7), 2358.

Mizobuchi, M., Ishidoh, K., & Kamemura, N. (2022). A comparison of cell death mechanisms of antioxidants, butylated hydroxyanisole and butylated hydroxytoluene. *Drug and Chemical Toxicology*, *45*(4), 1899-1906.

Molina-Montes, E., Uzhova, I., Verardo, V., Artacho, R., García-Villanova, B., Guerra-Hernández, E. J., Kapsokefalou, M., Malisova, O., Vlassopoulos, A., & Katidi, A. (2021). Impact of COVID-19 confinement on eating behaviours across 16 European countries: The COVIDiet cross-national study. *Food Quality and Preference*, *93*, 104231.

Nanditha, B., & Prabhasankar, P. (2008). Antioxidants in bakery products: a review. *Critical reviews in food science and nutrition*, *49*(1), 1-27.

Niehoff, N. M., Goldberg, M., & White, A. J. (2022). The Importance of Addressing Early-Life Environmental Exposures in Cancer Epidemiology. *Current epidemiology reports*, *9*(2), 49-65.

Nilsen-Nygaard, J., Fernández, E. N., Radusin, T., Rotabakk, B. T., Sarfraz, J., Sharmin, N., Sivertsvik, M., Sone, I., & Pettersen, M. K. (2021). Current status of biobased and biodegradable food packaging materials: Impact on food quality and effect of innovative processing technologies. *Comprehensive reviews in food science and food safety*, *20*(2), 1333-1380.

Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Lunts, A., Kreyling, W., & Cox, C. (2002). Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. *Journal of Toxicology and Environmental Health, Part A*, *65*(20), 1531-1543.

Ocagli, H., Lanera, C., Franzoi, M., Monachesi, C., Zgheib, R., Belluco, S., Dacasto, M., Gregori, D., & Baldi, I. (2024). Unveiling insights from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) portal. *Scientific data*, *11*(1), 1443.

Oliveira, T. C., Chamorro, F., Pereira, E., Sousa, S., Barroso, F., Delerue-Matos, C., Domingues, V. F., Barros, L., & Prieto, M. A. (2025). Risk assessment of replacing synthetic preservatives with natural ingredients. *EFSA Journal*, *23*, e231117.

Organization, W. H., & Cancer, I. A. f. R. o. (1986). Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation.

Oromiehie, A. Properties and Application of Multifunctional Composite Polypropylene-Based Films Incorporating a Combination of BHT, BHA and Sorbic Acid in Extending Donut Shelf-Life. *Molecules*.

Ott, M., Gogvadze, V., Orrenius, S., & Zhivotovsky, B. (2007). Mitochondria, oxidative stress and cell death. *Apoptosis*, *12*(5), 913-922.

Paramasivam, A., Murugan, R., Jeraud, M., Dakkumadugula, A., Periyasamy, R., & Arjunan, S. (2024). Additives in processed foods as a potential source of endocrine-disrupting chemicals: a review. *Journal of xenobiotics*, *14*(4), 1697-1710.

Parveen, B., Rajinikanth, V., & Narayanan, M. (2025). Natural plant antioxidants for food preservation and emerging trends in nutraceutical applications. *Discover Applied Sciences*, *7*(8), 845.

Pastoukhova, P. V. (2025). Eu green chemical legislation and its impact to cosmetic industry.

Peluso, I. (2022). Diet and exercise in lifestyle medicine: The hormetic effects of bioactive compounds on human health. *Current Opinion in Toxicology*, *30*, 100342.

Peluso, J., Martínez Chehda, A., Cuzziol Boccioni, A. P., Peltzer, P. M., Lajmanovich, R. C., Olivelli, M. S., De Geronimo, E., Aparicio, V., Gonzalez, F., & Valenzuela, L. (2025). The impact of dairy effluent on water quality and ecotoxicological effects on amphibian larvae. *Chemistry and Ecology*, *41*(4), 423-443.

Peng, L., Li, Z.-R., Green, R. S., Holzman, I. R., & Lin, J. (2009). Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *The Journal of nutrition*, *139*(9), 1619-1625.

Petcu, C. D., Mihai, O. D., Tăpăloagă, D., Gheorghe-Irimia, R.-A., Pogurschi, E. N., Militaru, M., Borda, C., & Ghimpețeanu, O.-M. (2023). Effects of plant-based antioxidants in animal diets and meat products: A review. *Foods*, *12*(6), 1334.

Pomeranz, J. L., Broad Leib, E. M., & Mozaffarian, D. (2024). Regulation of added substances in the food supply by the Food and Drug Administration Human Foods Program. *American Journal of Public Health*, *114*(10), 1061-1070.

Rafiq, M. S., Khan, J. A., Bukhari, A. A. S., Shafqat, S., Waheed, A., Abbas, M. Y., Aslam, M. W., Shaikh, I. I., Almaary, K. S., & Khan, M. S. (2025). Investigating the Wound Healing Potential of CuCO3 Nanoparticles in Alloxan-Induced Diabetic Albino Mice: An Experimental and In Silico Approach. *Biological Trace Element Research*, 1-17.

Rao, M. J., & Zheng, B. (2025). The role of polyphenols in abiotic stress tolerance and their antioxidant properties to scavenge reactive oxygen species and free radicals. *Antioxidants*, *14*(1), 74.

Reed, K. A. (2009). Identification of phenolic compounds from peanut skin using HPLC-MSn.

Ren, J., Li, Z., Li, X., Yang, L., Bu, Z., Wu, Y., Li, Y., Zhang, S., & Meng, X. (2025). Exploring the Mechanisms of the Antioxidants BHA, BHT, and TBHQ in Hepatotoxicity, Nephrotoxicity, and Neurotoxicity from the Perspective of Network Toxicology. *Foods*, *14*(7), 1095.

Roberts, M. S., Magnusson, B. M., Burczynski, F. J., & Weiss, M. (2002). Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. *Clinical pharmacokinetics*, *41*(10), 751-790.

Rodrigues, J. S., do Valle, C. P., Uchoa, A. F. J., Ramos, D. M., da Ponte, F. A. F., de Sousa Rios, M. A., de Queiroz Malveira, J., & Ricardo, N. M. P. S. (2020). Comparative study of synthetic and natural antioxidants on the oxidative stability of biodiesel from Tilapia oil. *Renewable Energy*, *156*, 1100-1106.

Santos, N. A., Cordeiro, A. M., Damasceno, S. S., Aguiar, R. T., Rosenhaim, R., Carvalho Filho, J. R., Santos, I. M., Maia, A. S., & Souza, A. G. (2012). Commercial antioxidants and thermal stability evaluations. *Fuel*, *97*, 638-643.

Savin, M., Vrkatić, A., Dedić, D., Vlaški, T., Vorgučin, I., Bjelanović, J., & Jevtic, M. (2022). Additives in children's nutrition—a review of current events. *International Journal of Environmental Research and Public Health*, *19*(20), 13452.

Session, T. (2007). Joint FAO/WHO Food Standards Programme Codex Alimentarius Commission. *Codex*.

Shahidi, F., & Zhong, Y. (2010a). Lipid oxidation and improving the oxidative stability. *Chemical society reviews*, *39*(11), 4067-4079.

Shahidi, F., & Zhong, Y. (2010b). Novel antioxidants in food quality preservation and health promotion. *European Journal of Lipid Science and Technology*, *112*(9), 930-940.

Singh, P., Saengerlaub, S., Abas Wani, A., & Langowski, H. C. (2012). Role of plastics additives for food packaging. *Pigment & Resin Technology*, *41*(6), 368-379.

Steffensen, I.-L., Fæste, C. K., Husøy, T., Knutsen, H. K., Mathisen, G. H., Ørnsrud, R., Agdestein, A., Bodin, J. E., Elvevoll, E. O., & Hessen, D. O. (2019). Ranking of substances for monitoring in foods, drinks and dietary supplements-based on risk and knowledge gaps.

Tamarin, S., Jung, H., LaMorte, J., Biesterveld, L., Piñero, G., Turchetta, G., Myers, M. S., Oberley-Deegan, R., & Eggler, A. L. (2026). An Antioxidant Cocktail of Tert-Butylhydroquinone and a Manganese Porphyrin Induces Toxic Levels of Oxidative Stress in Cancer Cells. *Antioxidants*, *15*(2), 165.

Umar, A., Khan, M. S., & Wajid, M. (2026a). Cobalt nanostructures induced hematotoxicity and renal toxicity in albino mice: an experimental and computational evaluation. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 1-21.

Umar, A., Khan, M. S., & Wajid, M. (2026b). Pharmacokinetics Evaluation and Hepatotoxic Effects of Cobalt Iodide Nanoplates on Liver Function in Albino Mice. *BioNanoScience*, *16*(3), 172.

Van Esch, G. (1986). Toxicology of tert-butylhydroquinone (TBHQ). *Food and Chemical Toxicology*, *24*(10-11), 1063-1065.

Veyrand, J., Marin-Kuan, M., Bezencon, C., Frank, N., Guérin, V., Koster, S., Latado, H., Mollergues, J., Patin, A., & Piguet, D. (2017). Integrating bioassays and analytical chemistry as an improved approach to support safety assessment of food contact materials. *Food Additives & Contaminants: Part A*, *34*(10), 1807-1816.

Wang, S., Zhang, H., Shi, X., Zhang, Q., Ren, Y., Chen, J., Wang, H., Wang, W., & Wang, Q. (2025). The reaction laws and toxicity effects of synthetic phenolic antioxidants (SPAs) in wastewater and atmosphere: A theoretical investigation. *Process Safety and Environmental Protection*, *200*, 107324.

Wang, Y., Su, H., Liu, N., Yang, N., & Gao, P. (2025). Distribution of synthetic antioxidants in outdoor and educational indoor dusts and assessment of human exposure. *Environmental Geochemistry and Health*, *47*(5), 183.

Wang, Z., Wang, Y., Zhang, J., Feng, G., Miao, S., Lu, R., Tian, X., & Ye, Y. (2025). Antioxidant intervention against microplastic hazards. *Antioxidants*, *14*(7), 797.

Whisel, A. M. (2025). *The Influence of tert-Butylhydroquinone (TBHQ) on ACOD1/IRG1-Driven Inflammatory Pathways* Clemson University].

Whisel, A. M., & Rice, C. D. (2025). Tert-butylhydroquinone (TBHQ) suppresses lps-and poly (I: C)-induced RAW 264.7 macrophage activation through reduced NF-κB/type 1 interferon and enhanced antioxidant-related pathways. *Toxics*, *13*(10), 883.

Xu, J., Hao, Y., Yang, Z., Li, W., Xie, W., Huang, Y., Wang, D., He, Y., Liang, Y., & Matsiko, J. (2022). Rubber antioxidants and their transformation products: environmental occurrence and potential impact. *International Journal of Environmental Research and Public Health*, *19*(21), 14595.

Xu, X., Liu, A., Hu, S., Ares, I., Martínez-Larrañaga, M.-R., Wang, X., Martínez, M., Anadón, A., & Martínez, M.-A. (2021). Synthetic phenolic antioxidants: Metabolism, hazards and mechanism of action. *Food chemistry*, *353*, 129488.

Xu, Y., Ding, T., Zhu, Q., Tao, L., Liu, S.-S., Hu, L., & Liao, C. (2024). Ecological risk of synthetic phenolic antioxidants: A study based on their spatial distribution in water, sediment, and soil from the Yangtze River Delta, China. *Environmental Research*, *262*, 119920.

Yang, X., Hayat, K., Chen, R., Liu, Y., Bai, X., & Liu, W. (2025). Enantioselective transplacental transfer of xenobiotics: mechanisms, plasma protein binding, and health implications for fetal development. *Archives of Toxicology*, *99*(9), 3689-3705.

Zhang, L.-H., Chen, F., Zhang, X.-M., Zhang, X., Liang, B., Zhang, Z.-F., Bai, S.-S., Li, Y.-F., & Ren, N.-Q. (2025). Substituted diphenylamine antioxidants and synthetic phenolic antioxidants in leachate from domestic landfills in China: Occurrence and removal via treatment. *Journal of Hazardous Materials*, 140474.

Zhang, X. J., Diao, M. n., & Zhang, Y. F. (2023). A review of the occurrence, metabolites and health risks of butylated hydroxyanisole (BHA). *Journal of the Science of Food and Agriculture*, *103*(13), 6150-6166.

Zhang, Y., Du, B., Ge, J., Liu, L., Zhu, M., Li, J., & Zeng, L. (2020). Co-occurrence of and infant exposure to multiple common and unusual phenolic antioxidants in human breast milk. *Environmental Science & Technology Letters*, *7*(3), 206-212.

Zhao, H.-J., Xu, J.-K., Yan, Z.-H., Ren, H.-Q., & Zhang, Y. (2020). Microplastics enhance the developmental toxicity of synthetic phenolic antioxidants by disturbing the thyroid function and metabolism in developing zebrafish. *Environment International*, *140*, 105750.

Zhao, Y.-L., Zhao, W., Liu, M., Liu, L., & Wang, Y. (2020). TBHQ-overview of multiple mechanisms against oxidative stress for attenuating methamphetamine-induced neurotoxicity. *Oxidative medicine and cellular longevity*, *2020*(1), 8874304.

Abbas, M. Y., Umar, A., Aslam, M. W., ul Ghafoor, W., Nazeer, N., Khan, M. U., & Ali, H. (2025). Computational and experimental assessment of the toxicological effects of copper oxide nanoparticles on haematological and biochemical parameters in albino mice. *Toxicology research*, *14*(5), tfaf139.

Aslam, M. W., Umar, A., Khan, M. S., Wajid, M., & Khan, M. U. (2025b). Impact of Copper Carbonate Nanoparticles on Hematological, Liver, and Kidney Function, Lipid Profile, and Hormonal Regulation in Albino Mice: A Combined Experimental and Computational Analysis. *BioNanoScience*, *15*(1), 1–23.

Umar, A., Khan, M. S., Wajid, M., & Khan, M. U. (2024a). Dose-Dependent Effects of Cobalt Nanoparticles on Antioxidant Systems, Hematological Parameters, and Organ Morphology in Albino Mice. *BioNanoScience*, 1–21.

Umar, A., Khan, M. S., Wajid, M., & Ullah, H. (2024b). Biocompatibility, Antimicrobial Efficacy, and Therapeutic Potential of Cobalt Carbonate Nanoparticles in Wound Healing, Sex Hormones, and Metabolic Regulation in Diabetic Albino Mice. *Biochemical and Biophysical Research Communications*, 150773.

Umar, A., Khan, M. S., Hassan, W., Ullah, H., Sabri, S., Ali, A., & Gurbanova, L. (2025a). Pharmaceutical Potential of Cobalt Iodide Nanoparticles in Enhancing Wound Healing and Modulating Endocrine, Immune, Metabolic and Antibacterial Functions. *Biochemical and Biophysical Research Communications*, 152320.