Food and Chemical Toxicology
Volume 1, Number 2, 2022

Chemical Food Additives and Human Health: Toxicological Mechanisms, Exposure Assessment, and Risk Evaluation

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Abstract

Article history:
Received: 5 July 2022
Revised: 3 August 2022
Accepted: 25 September 2022
Published: 30 December 2022

Keywords:
Acceptable daily intake;
Dietary exposure;
Food additives;
Risk assessment;
Toxicity mechanisms;
Ultra-processed foods.

Identifier:
Zera Open
Page: 89-105
https://zeraopen.com/journal/fct

This study examines the safety of chemical food additives in relation to toxicological mechanisms, dietary exposure, and risk evaluation frameworks. Food additives are widely used in processed foods to enhance quality and shelf life, yet their long-term health implications remain a subject of concern. Using a qualitative Systematic Literature Review (SLR) approach, this study synthesizes recent research to identify key patterns linking additive functions, cumulative exposure, and biological effects. The findings indicate that dietary intake of multiple additives is continuous and may exceed simplified regulatory assumptions based on individual compounds. At the molecular level, mechanisms such as oxidative stress and metabolic disruption are identified as key pathways of toxicity. Furthermore, existing risk assessment models, including acceptable daily intake, may not fully capture combined exposure and real-world consumption patterns. This study highlights the need for more integrative approaches to food additive safety evaluation and risk management.

1. Introduction

The increasing reliance on processed and ultra-processed foods in modern diets has led to a substantial rise in the use of chemical food additives, including preservatives, colorants, emulsifiers, and artificial sweeteners. These substances are intentionally incorporated into food products to enhance shelf life, stability, taste, and visual appeal. Regulatory authorities have established safety evaluation frameworks to ensure that such additives do not pose significant health risks under defined conditions of use. However, growing scientific and public health concerns suggest that the long-term implications of continuous dietary exposure to multiple additives may not be fully understood (Pressman et al., 2017; Trasande et al., 2018).

From a toxicological perspective, food additives are generally assessed based on controlled experimental conditions that determine safe exposure thresholds, commonly expressed as Acceptable Daily Intake (ADI). These thresholds are derived from toxicological studies using safety factors to account for interspecies and individual variability. While this approach provides a structured basis for regulatory approval, it primarily evaluates individual compounds in isolation and may not adequately reflect real-world consumption patterns characterized by simultaneous exposure to multiple additives (Fitch et al., 2021; Stanković & Zrnić-Ćirić, 2021). This discrepancy raises questions regarding the robustness of existing risk assessment models in capturing cumulative and long-term exposure risks.

At the molecular level, emerging evidence indicates that certain food additives may induce biological effects through mechanisms such as oxidative stress, inflammation, and disruption of metabolic processes. These mechanisms are similar to those observed in broader chemical toxicology, suggesting that even substances deemed safe within regulatory limits may contribute to subtle but significant physiological changes over prolonged periods (Vinken et al., 2020; Youn & Choi, 2022). In particular, recent studies have explored the potential impact of additives such as emulsifiers and artificial sweeteners on gut microbiota, metabolic regulation, and systemic health outcomes, highlighting the complexity of additive-related toxicity beyond traditional endpoints (Cox et al., 2021; Ali et al., 2021).

In addition to mechanistic concerns, epidemiological and dietary studies have linked high consumption of ultra-processed foods—major sources of food additives—to adverse health outcomes, including metabolic disorders and increased cancer risk. Although these associations do not establish direct causality between specific additives and health effects, they underscore the importance of considering overall dietary exposure patterns and their cumulative impact on human health (Fiolet et al., 2018; Pagliai et al., 2021). These findings challenge the assumption that compliance with regulatory limits alone is sufficient to ensure long-term safety.

Despite the expanding body of research, existing studies often remain fragmented, focusing either on specific additives, isolated toxicological mechanisms, or regulatory frameworks without integrating these dimensions into a unified perspective. This fragmentation limits the ability to comprehensively evaluate the safety of food additives in the context of real-world exposure scenarios. Furthermore, variations in methodological approaches and regulatory standards across regions contribute to inconsistencies in safety evaluation outcomes.

Accordingly, there is a need for a systematic and integrative synthesis that links dietary exposure, molecular toxicity mechanisms, and risk assessment frameworks within a single analytical framework. Such an approach is essential for critically assessing whether current safety evaluation systems adequately reflect the complexity of additive exposure in modern food systems.

Therefore, this study aims to systematically review and synthesize recent literature on chemical food additives, focusing on their toxicological mechanisms, dietary exposure patterns, and risk evaluation frameworks. By employing a qualitative Systematic Literature Review (SLR) approach, this study seeks to provide a comprehensive understanding of how food additives interact with biological systems and to evaluate the extent to which existing regulatory models capture potential long-term health risks.

From a methodological perspective, this study adopts a qualitative SLR to integrate findings from peer-reviewed journal articles and authoritative regulatory reports published in recent years. The analysis emphasizes thematic synthesis to identify consistent patterns and conceptual relationships across studies, providing a structured foundation for evaluating the safety and toxicological implications of food additives in contemporary diets.

2. Literature Review

2.1. Classification and Functional Roles of Food Additives

Food additives encompass a wide range of chemical substances intentionally incorporated into food products to improve preservation, texture, flavor, and visual appeal. Early studies categorize additives into functional groups such as preservatives, colorants, emulsifiers, and sweeteners, each serving distinct technological purposes within food systems. These classifications provide a foundational understanding of how additives contribute to food processing and industrial production.

Subsequent research expands this perspective by emphasizing the increasing diversity and complexity of additives used in modern food systems. Advances in food technology have introduced novel compounds, including nano-scale additives and multifunctional ingredients, which enhance product stability and performance but also raise new safety considerations (Rather et al., 2017; Kumar et al., 2019). The growing prevalence of such additives reflects the shift toward highly processed foods, where multiple additives are often used simultaneously.

More recent literature highlights that the functional benefits of additives are closely linked to their chemical properties and interactions within food matrices. Comprehensive reviews indicate that additives not only influence product quality but also affect digestion, absorption, and metabolic responses in the human body (Awuchi et al., 2020; Wu et al., 2022). This evolving understanding underscores the importance of examining food additives beyond their technological roles, considering their broader implications for human health.

2.2. Toxicological Mechanisms of Food Additives

The toxicological effects of food additives are increasingly understood through molecular and cellular mechanisms that parallel broader chemical toxicology. Foundational research on oxidative stress demonstrates that exposure to certain chemical compounds can lead to the generation of reactive oxygen species, resulting in cellular damage and disruption of biological functions. These mechanisms provide a baseline for understanding additive-related toxicity.

Further studies have identified that specific additives may interfere with metabolic pathways, enzyme activity, and cellular signaling processes. Experimental and review-based research indicates that compounds such as artificial sweeteners and nano-additives can induce metabolic alterations and cytotoxic effects under certain exposure conditions (Samoilov et al., 2019; Youn & Choi, 2022). These findings suggest that even regulated substances may exhibit biological activity that warrants closer examination.

Recent advances in toxicology have introduced frameworks such as adverse outcome pathways (AOPs), which link molecular-level interactions to observable health outcomes. This approach enables a more systematic understanding of how chemical exposures translate into physiological effects, providing a structured basis for evaluating additive safety (Vinken et al., 2020). The integration of mechanistic insights into risk assessment represents a significant development in modern toxicology.

2.3. Dietary Exposure and Consumption Patterns

Dietary exposure to food additives is primarily driven by the consumption of processed and ultra-processed foods, which often contain multiple additives within a single product. Early research highlights that increasing industrialization of food production has led to higher additive intake across populations, particularly in urbanized and high-income settings. These trends establish the foundation for understanding exposure dynamics.

Subsequent studies provide quantitative and epidemiological insights into the relationship between processed food consumption and health outcomes. Large-scale cohort and systematic review studies demonstrate associations between high intake of ultra-processed foods and increased risks of metabolic disorders and cancer, suggesting that additive exposure may contribute to broader dietary risk profiles (Fiolet et al., 2018; Pagliai et al., 2021). While causality remains complex, these findings emphasize the importance of considering cumulative dietary exposure.

More recent literature further explores the variability of exposure across populations, influenced by dietary habits, socioeconomic factors, and regulatory environments. Reviews indicate that exposure levels may differ significantly depending on consumption patterns and food system structures, highlighting the need for context-specific risk assessments (Cox et al., 2021; Wu et al., 2022). This variability complicates the evaluation of additive safety on a global scale.

2.4. Risk Assessment and Regulatory Frameworks

The safety of food additives is primarily evaluated through regulatory frameworks that rely on toxicological testing and exposure assessment. Early approaches to risk evaluation introduced the concept of Acceptable Daily Intake (ADI), which defines the maximum amount of a substance that can be consumed daily over a lifetime without appreciable health risk (Pressman et al., 2017). This concept remains central to additive regulation.

Subsequent developments in risk assessment have incorporated more structured and quantitative methods, including the use of safety factors, exposure modeling, and hazard identification techniques. Regulatory agencies have also developed standardized guidelines to ensure consistency in safety evaluation across different additives and food systems (Fürst et al., 2019; Stanković & Zrnić-Ćirić, 2021). These frameworks aim to balance technological benefits with public health protection.

More recent research critically evaluates the limitations of existing regulatory approaches, particularly in relation to cumulative exposure and combined effects of multiple additives. Studies emphasize that traditional risk assessment models often focus on single substances and may not adequately capture real-world exposure scenarios involving complex mixtures (Fitch et al., 2021; EFSA Scientific Committee, 2021). This has led to increasing calls for more integrative and dynamic risk assessment strategies that reflect contemporary food consumption patterns.

3. Methods

This study adopts a qualitative Systematic Literature Review (SLR) approach to examine chemical food additives in relation to their toxicological mechanisms, dietary exposure patterns, and risk evaluation frameworks. The SLR method is selected to provide a structured and integrative synthesis of existing scientific knowledge without generating new empirical data. This approach is particularly appropriate given the complexity of food additive safety, which involves the interaction of chemical properties, biological responses, and regulatory assessments across multiple disciplines, including toxicology, food science, and public health.

The literature search was conducted systematically using academic databases and publisher platforms. The search strategy employed combinations of keywords such as "food additives," "toxicity," "oxidative stress," "dietary exposure," "risk assessment," "acceptable daily intake," and "regulatory toxicology" to capture studies addressing both mechanistic and regulatory aspects of food additive safety. To ensure relevance and recency, the search was limited to publications from 2017 to 2022, while allowing selective inclusion of highly cited foundational studies where necessary to support conceptual explanations.

The selection process involved screening titles, abstracts, and full-text articles to identify studies directly related to food additives and their implications for human health. Peer-reviewed journal articles and authoritative institutional reports were prioritized to ensure academic rigor and policy relevance. Studies focusing solely on non-food chemical exposures or lacking clear discussion of toxicity mechanisms or risk evaluation were excluded. In addition, preference was given to review articles, systematic reviews, and studies that provide comprehensive discussions of exposure, mechanism, and regulatory assessment, as these contribute to a more integrative synthesis.

The selected literature was analyzed using qualitative thematic synthesis, which involved identifying recurring patterns, conceptual relationships, and convergent findings across studies. The analysis was structured around key thematic dimensions, including types and functions of food additives, molecular mechanisms of toxicity, dietary exposure patterns, and regulatory risk assessment frameworks such as acceptable daily intake. Rather than applying quantitative aggregation or statistical meta-analysis, the study emphasizes conceptual integration to develop a coherent understanding of how food additives interact with biological systems and how their safety is evaluated within current regulatory frameworks.

4. Results

This section presents and interprets the key findings derived from the systematic literature review on chemical food additives, focusing on their functional roles, toxicological mechanisms, dietary exposure patterns, and risk evaluation frameworks. Rather than reporting empirical measurements, the analysis synthesizes recurring conceptual patterns identified across the reviewed literature. The findings highlight that the safety of food additives is shaped by the interaction between technological functions, biological effects, and regulatory evaluation processes.

4.1. Key Themes Identified from the Literature

The reviewed literature indicates that food additives serve essential technological functions in modern food systems, yet their safety cannot be evaluated solely based on intended use. Instead, safety emerges from the balance between functional benefits, exposure levels, and biological responses. Importantly, the literature consistently emphasizes that additive-related risks are influenced by cumulative exposure and interactions between multiple compounds rather than by isolated substances..

Table 1. Key Themes in Food Additives, Toxicity Mechanisms, and Exposure Patterns

Analytical Dimension	Key Findings from Literature	Toxicological Implications
Functional roles	Additives improve preservation, stability, taste, and appearance in processed foods	Increased reliance on chemical additives in modern diets (Awuchi et al., 2020)
Additive diversity	Expansion of additive types, including nano-additives and synthetic compounds	Greater complexity in safety evaluation (Rather et al., 2017; Wu et al., 2022)
Dietary exposure	Processed and ultra-processed foods are primary sources of additive intake	Continuous and multi-source exposure (Fiolet et al., 2018; Pagliai et al., 2021)
Cumulative intake	Multiple additives consumed simultaneously in daily diets	Potential combined and synergistic effects (Cox et al., 2021; Fitch et al., 2021)
Oxidative stress	Certain additives induce reactive oxygen species and cellular stress	Initiation of cellular damage pathways (Youn & Choi, 2022)
Metabolic disruption	Additives may interfere with metabolic and enzymatic processes	Altered physiological regulation (Samoilov et al., 2019; Ali et al., 2021)
Advanced toxicology	Use of adverse outcome pathways (AOP) to link molecular events to health effects	Improved mechanistic understanding (Vinken et al., 2020)
Health outcomes	High intake of additive-rich foods associated with chronic disease risk	Long-term public health implications (Trasande et al., 2018; Pagliai et al., 2021)
Regulatory evaluation	Safety assessed through ADI and toxicological testing frameworks	Standardized but simplified safety models (Pressman et al., 2017; Stanković & Zrnić-Ćirić, 2021)

4.2. Integrated Safety and Risk Evaluation Framework

Beyond individual findings, the literature reveals a structured relationship between additive use, exposure, biological response, and regulatory evaluation. Food additive safety is not determined solely by toxicity or exposure independently, but by the interaction between these elements within established regulatory frameworks.

This creates a “safety paradox,” where substances considered safe under controlled thresholds may still pose risks under cumulative and long-term exposure conditions.

Table 2. Conceptual Framework of Food Additive Safety and Toxicological Risk.

Evaluation Component	Regulatory Perspective	Toxicological Reality	Risk Implication
Additive approval	Substances approved based on toxicological testing	Testing often conducted on single compounds	Limited reflection of real-world exposure
Exposure threshold (ADI)	Defined safe intake level over lifetime	Does not fully account for cumulative intake	Potential underestimation of risk
Consumption pattern	Assumes controlled and moderate intake	High consumption of processed foods increases exposure	Elevated long-term exposure risk
Mechanistic assessment	Focus on observable toxic endpoints	Subtle molecular effects (e.g., oxidative stress) may occur earlier	Hidden or delayed toxicity
Combined effects	Typically evaluated individually	Multiple additives consumed simultaneously	Synergistic or additive effects possible
Regulatory framework	Standardized and consistent guidelines	Variability in population exposure and sensitivity	Context-dependent risk outcomes

4.3. Interpretation of Key Findings

The synthesis indicates that the safety of food additives is inherently conditional, depending on the interaction between exposure levels, biological responses, and regulatory assumptions. While additives are approved based on established toxicological thresholds, real-world dietary patterns characterized by frequent consumption of processed foods may lead to cumulative exposure that exceeds these simplified models.

A key insight is that molecular-level mechanisms, particularly oxidative stress and metabolic disruption, provide a consistent link between additive exposure and potential health effects. These mechanisms suggest that even low-dose, long-term exposure may contribute to subtle biological changes that are not fully captured by traditional safety assessments.

Furthermore, the findings highlight a gap between regulatory evaluation and toxicological complexity. Existing frameworks offer structured and standardized approaches to safety assessment, yet they may not fully incorporate combined exposure effects, variability across populations, and evolving scientific understanding of toxicity mechanisms. This reinforces the need for more integrative approaches that align regulatory practices with real-world exposure conditions.

5. Discussion

The findings highlight that the safety of food additives is inherently conditional and cannot be fully understood through isolated toxicological testing alone. While regulatory frameworks rely on controlled exposure thresholds, real-world consumption patterns involve frequent and simultaneous intake of multiple additives, particularly through processed foods. This creates a gap between regulatory assumptions and actual exposure conditions, suggesting that current safety evaluations may underestimate cumulative and long-term risks.

At the mechanistic level, the presence of consistent pathways such as oxidative stress and metabolic disruption indicates that additive-related toxicity may develop gradually and systemically rather than through acute effects. This reinforces the need to move beyond traditional endpoint-based assessments toward more integrative approaches that consider combined exposure, variability in dietary habits, and subtle biological responses. Overall, the findings suggest that improving food additive safety requires aligning regulatory models with the complexity of real-world exposure and evolving toxicological knowledge.

6. Conclusion

This study demonstrates that chemical food additives, while essential for modern food production, present a complex safety challenge shaped by the interaction between technological functions, exposure patterns, and biological responses. The findings indicate that dietary exposure to additives is continuous and often involves multiple compounds, particularly in diets dominated by processed foods. This creates conditions where cumulative intake may exceed simplified assumptions underlying current safety evaluations.

From a conceptual perspective, this study integrates toxicological mechanisms, dietary exposure, and regulatory risk assessment into a unified framework for evaluating food additive safety. The analysis highlights that mechanisms such as oxidative stress and metabolic disruption provide important insight into how long-term exposure may contribute to adverse health outcomes. This integrated perspective emphasizes that safety should be evaluated not only at the level of individual substances but also in the context of combined exposure and real-world consumption patterns.

In practical terms, the findings underscore the need to strengthen risk assessment approaches by incorporating cumulative exposure, population variability, and advances in mechanistic toxicology. Future research may focus on developing more dynamic evaluation models, conducting longitudinal exposure studies, and refining regulatory frameworks to better reflect contemporary dietary behaviors. Such efforts are essential for improving food safety management and ensuring that regulatory standards remain aligned with emerging scientific evidence.

References

Ali, A., More, T. A., & Shaikh, Z. (2021). Artificial sweeteners and their health implications: A review. *Biosciences Biotechnology Research Asia*, 18(2), 227–237.

Awuchi, C. G., Twinomuhwezi, H., Igwe, V. S., & Amagwula, I. O. (2020). Food additives and food preservatives for domestic and industrial food applications. *Journal of Animal Health*, 2(1), 1–16.

Cox, S., Sandall, A., Smith, L., Rossi, M., & Whelan, K. (2021). Food additive emulsifiers: A review of their role in foods, legislation and classifications, presence in food supply, dietary exposure, and safety assessment. *Nutrition Reviews*, 79(6), 726–741.

EFSA Panel on Additives and Products or Substances used in Animal Feed. (2018). Guidance on the assessment of the efficacy of feed additives. *EFSA Journal*, 16(5), e05274.

EFSA Scientific Committee. (2021). Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: Human and animal health. *EFSA Journal*, 19(8), e06768.

Fiolet, T., Srour, B., Sellem, L., Kesse-Guyot, E., Allès, B., Méjean, C., & Touvier, M. (2018). Consumption of ultra-processed foods and cancer risk: Results from the NutriNet-Santé prospective cohort. *BMJ*, 360, k322.

Fitch, S. E., Payne, L. E., van de Ligt, J. L., Doepker, C., Handu, D., Cohen, S. M., & Wikoff, D. (2021). Use of acceptable daily intake (ADI) as a health-based benchmark in nutrition research studies that consider the safety of low-calorie sweeteners: A systematic map. *BMC Public Health*, 21(1), 956.

Fürst, P., Milana, M. R., Pfaff, K., Tlustos, C., Vleminckx, C., Arcella, D., & Afonso, A. (2019). Risk evaluation of chemical contaminants in food in the context of RASFF notifications: Rapid assessment of contaminant exposure tool (RACE). *EFSA Journal*, 16(5), e1625E.

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

Pagliai, G., Dinu, M., Madarena, M. P., Bonaccio, M., Iacoviello, L., & Sofi, F. (2021). Consumption of ultra-processed foods and health status: A systematic review and meta-analysis. *British Journal of Nutrition*, 125(3), 308–318.

Pașca, C., Coroian, A., & Socaci, S. (2018). Risks and benefits of food additives: A review. *Bulletin UASVM Food Science and Technology*, 75(2), 82–89.

Pressman, P., Clemens, R., Hayes, W., & Reddy, C. (2017). Food additive safety: A review of toxicologic and regulatory issues. *Toxicology Research and Application*, 1, 2397847317723572.

Rather, I. A., Koh, W. Y., Paek, W. K., & Lim, J. (2017). The sources of chemical contaminants in food and their health implications. *Frontiers in Pharmacology*, 8, 830.

Samoilov, A. V., Suraeva, N. M., Zaitseva, M. V., Kurbanova, M. N., & Stolbova, V. V. (2019). Comparative assessment of artificial sweeteners toxicity via express biotest. *Health Risk Analysis*, (2), 83–90.

Stanković, I., & Zrnić-Ćirić, M. (2021). Food additives: Risk analysis and legislation. *Arhiv za Farmaciju*, 71(1), 22–34.

Trasande, L., Shaffer, R. M., Sathyanarayana, S., Council on Environmental Health, Lowry, J. A., Ahdoot, S., & Woolf, A. D. (2018). Food additives and child health. *Pediatrics*, 142(2), e20181410.

Vinken, M., Kramer, N., Allen, T. E., Hoffmans, Y., Thatcher, N., Levorato, S., & Rietjens, I. M. (2020). The use of adverse outcome pathways in the safety evaluation of food additives. *Archives of Toxicology*, 94(3), 959–966.

Wu, L., Zhang, C., Long, Y., Chen, Q., Zhang, W., & Liu, G. (2022). Food additives: From functions to analytical methods. *Critical Reviews in Food Science and Nutrition*, 62(30), 8497–8517.

Youn, S. M., & Choi, S. J. (2022). Food additive zinc oxide nanoparticles: Dissolution, interaction, fate, cytotoxicity, and oral toxicity. *International Journal of Molecular Sciences*, 2he3(11), 6074.