Supplementary Document S1: Complete Additive Risk Scoring Database with Full Justifications and Citations

Potassium Bromate
Risk Score: 10
Category: Flour Treatment Agent/Dough Conditioner

Potassium bromate is a potent carcinogen that exhibits a clear dose-response relationship, particularly concerning the development of renal adenocarcinomas and adenomas. Oral exposure has been shown to induce these kidney tumors at concentrations as low as 125 ppm, while pre-cancerous dysplastic foci in the kidneys emerge at doses higher than 30 ppm. Furthermore, high-level exposure at 500 ppm is associated with a significantly increased incidence of thyroid follicular tumors and peritoneal mesotheliomas, alongside systemic health impacts such as inhibited body weight gain and reduced survival time. Statistical modeling from these findings suggests that the virtually safe dose to minimize cancer risk is extremely low, highlighting the compound's high level of toxicity and its broad impact on the renal, thyroid, and abdominal systems. (1)

Regulatory Status: Potassium Bromate is banned in the European Union (1990), Canada (1994), United Kingdom, Brazil, India (2016), China, Nigeria, Sri Lanka, Argentina, Peru, South Korea, Australia, and New Zealand. It is legal in the United States but banned in California (effective 2027) (2).

Dose/Context Qualifiers: Carcinogenic effects are observed at chronic low-dose exposure. Although potassium bromate decomposes during baking, residual levels have been detected in commercial bread products, particularly when baking time or temperature is insufficient.

Justification for Risk Score: A maximum score of 10 reflects conclusive animal carcinogenicity evidence, genotoxic mechanisms, international regulatory bans, and continued human exposure risk in jurisdictions where use remains permitted (1, 2, 3).

Acrylamide
Risk Score: 10
Category: Processing Contaminant

Acrylamide is recognized as a significant food contaminant found in baked and fried carbohydrate-rich foods, such as French fries, potato chips, and bread, as well as in beverages

like coffee. Although human epidemiological studies regarding dietary intake remain largely inconclusive due to challenges in estimating intake levels, experimental animal data provides sufficient evidence of its carcinogenicity. This is further supported by recent bioassays demonstrating the carcinogenic effects of both acrylamide and its electrophilic metabolite, glycidamide (4).

Regulatory Status: No specific ban exists; however, the European Union established benchmark levels through Commission Regulation 2017/2158 to drive industry mitigation efforts (5).

Dose/Context Qualifiers: Analysis of hemoglobin (Hb) adducts in adults reveals that humans undergo chronic, "unavoidable" exposure to acrylamide, with daily intakes estimated to reach approximately 100µg. This exposure is directly linked to the heating of foodstuffs at elevated temperatures, as acrylamide is not detectable in unheated or boiled foods. At the same time, protein-rich foods show moderate levels of the compound, carbohydrate-rich products, such as potatoes, beetroot, and crispbread, exhibit significantly higher concentrations, ranging from 150 to 4000µg/kg (6).

Justification for Risk Score: A maximum score of 10 is warranted based on robust animal carcinogenicity data, genotoxic mechanisms involving DNA adduct formation, and widespread unavoidable human dietary exposure (4, 6).

Trans Fats (Partially Hydrogenated Oils)
Risk Score: 10
Category: Processing Byproduct/Modified Fat

Health Impacts: Industrial trans fatty acids, produced through partial hydrogenation of vegetable oils, profoundly disrupt lipid metabolism. They simultaneously elevate low-density lipoprotein (LDL) cholesterol and lower high-density lipoprotein (HDL) cholesterol—a uniquely atherogenic lipid profile (7). Trans fats promote systemic inflammation (8), endothelial dysfunction (8), and insulin resistance (8). Epidemiological evidence also demonstrates a strong dose-response relationship with coronary heart disease (8).

Regulatory Status: Under FDA regulation, use of trans fats from PHOs was no longer allowed since January 1, 2021(9), and globally, the World Health Organization (WHO) recommends a

mandatory limit of 2g of trans fat per 100g of total fat or a total ban on partially hydrogenated oils (PHOs). As of 2025, approximately 60 countries have implemented these best-practice policies, protecting 46% of the global population (10).

Dose/Context Qualifiers: Industrial trans fat consumption, even at minimal levels (2–3% of total calories), significantly increases cardiovascular and metabolic risk. Research in murine models shows that trans fats are more hepatotoxic than calorically identical saturated fats, leading to higher serum alanine aminotransferase (ALT) levels and marked insulin resistance. This metabolic damage is linked to a fivefold increase in hepatic IL-1β gene expression, indicating a potent inflammatory response (8).

Justification for Risk Score: A maximum score of 10 reflects unequivocal human evidence linking trans fat intake to cardiovascular mortality, strong mechanistic understanding, and regulatory consensus resulting in widespread bans (7, 8, 9, 10).

Red 3 (Erythrosine)
Risk Score: 10
Category: Synthetic Azo Dye/Artificial Color

Health Impacts: FD & C Red No. 3 (erythrosine) is classified as a carcinogen due to its ability to induce thyroid follicular cell hypertrophy, hyperplasia, and adenomas, as demonstrated in chronic animal feeding studies. In these laboratory models, high-dose exposure over an extended period consistently leads to increased thyroid weights and cellular abnormalities, particularly in males. While industry groups have historically argued that the biological mechanism causing these rat tumors does not translate to human physiology, the additive's proven ability to trigger such growths is the primary driver for its recent federal ban under the Delaney Clause (11).

Regulatory Status: As of January 2025, the FDA has officially banned Red Dye No. 3 from the U.S. food supply and ingested medications, closing a decades-long regulatory gap that previously only prohibited the dye in cosmetics and topical drugs. This action, prompted by the Delaney Clause after studies linked the substance to cancer in laboratory rats, requires food manufacturers to reformulate products by January 2027 and drug makers to comply by January

2028. While international bodies and industry groups have previously defended its safety in humans, the U.S. now joins California and much of the European Union in restricting the dye, citing the legal necessity to remove known carcinogens from the food chain regardless of the specific biological mechanism (12).

Dose/Context Qualifiers: Human exposure to Red 3 occurs through the ingestion of dyed products like maraschino cherries, candies, and oral medications. Concerns are highest regarding cumulative exposure in children, who consume more of the dye on a bodyweight basis than adults. The most severe health outcomes in studies were associated with high-dose chronic ingestion (e.g., 4.0% dietary concentration) (11).

Justification for Risk Score: A maximum score of 10 is assigned based on clear evidence of carcinogenicity in animal studies, regulatory recognition of cancer risk leading to partial bans, and the regulatory inconsistency of permitting use in food while banning in cosmetics (11, 12).

Cyclamate
Risk Score: 10
Category: Artificial Sweetener

Health Impacts: Cyclamates are categorized as non-nutritive sweeteners that have shown evidence of testicular toxicity in animal models, specifically inducing testicular atrophy in rats at high dietary doses (approx. 400 mg/kg per day). While early studies observed some benign and malignant bladder tumors in rats, the incidences were often not statistically significant, and results from bladder implantation studies are difficult to interpret due to the carcinogenic effects of the pellets themselves. A critical factor in cyclamate toxicity is its biotransformation by gastrointestinal microflora into cyclohexylamine. This metabolite has distinct toxicological properties, including the ability to reduce sperm counts and motility in rats, though no treatment-related malformations (teratogenicity) have been consistently demonstrated in mammals (13).

Regulatory Status: Cyclamate was banned in the United States in 1970 following concerns over its carcinogenic potential. However, it remains approved for use in over 55 countries, including Australia, Canada (for table-top use), and the European Union. Global health authorities, including the WHO/FAO Joint Expert Committee on Food Additives, have established an Acceptable Daily Intake (ADI) of 11 mg/kg bw. There are currently no national or international occupational exposure limits for cyclamic acid or its salts in workplace air (13).

Dose/Context Qualifiers: The potential for toxicity is highly dependent on interindividual variation in metabolism, as only some humans are "converters" capable of transforming cyclamate into the more toxic cyclohexylamine. While dietary intake studies in Europe and Brazil show that most consumers remain well below the ADI, specific populations such as diabetic patients or high consumers of diet soft drinks may reach higher exposure levels (13).

Justification for Risk Score: A maximum score of 10 reflects the U.S. regulatory determination of sufficient cancer risk to warrant a permanent ban, reproductive toxicity evidence, and the regulatory principle that carcinogens should not be intentionally added to food regardless of dose (13).

Benzo[a]pyrene
Risk Score: 10
Category: Processing Contaminant (Polycyclic Aromatic Hydrocarbon)

Health Impacts: Benzo[a]pyrene (B[a]P) is a potent carcinogen formed during the incomplete combustion of organic materials like wood, tobacco, and grilled foods. Its toxicity stems from metabolic activation by cytochrome P450 enzymes into the reactive metabolite BPDE, which binds to DNA to form stable adducts. These adducts cause mutations in critical genes such as p53, leading to malignant transformations. Beyond multi-organ cancer (notably lung, forestomach, and mammary tumors), recent research links B[a]P to neurotoxicity, impaired fertility, and the production of damaging reactive oxygen species (ROS) (14).

Regulatory Status: Regulatory frameworks for Benzo[a]pyrene (B[a]P) vary internationally but reflect its status as a high-priority toxin. The European Union enforces strict maximum levels for B[a]P in specific food categories, such as oils and smoked products, and sets an atmospheric target value of 1 ng/m³ (14). In the United States, the Environmental Protection Agency (EPA) manages B[a]P through an extensive range of statutes, including the Clean Air Act as a Hazardous Air Pollutant, the Safe Drinking Water Act, and the Clean Water Act as a priority pollutant (15).

Dose/Context Qualifiers: Exposure occurs through air, water, soil, and diet, with levels varying significantly based on context. Dietary exposure is highest in charcoal-grilled or heavily smoked meats, where oil-based roasting produces more B[a]P than water-based cooking. Occupational environments, such as aluminum plants or coke ovens, present extreme risks with concentrations

thousands of times higher than urban air. Because B[a]P is a genotoxic carcinogen that directly damages DNA, health authorities maintain that there is no safe threshold for exposure (14).

Justification for Risk Score: A maximum risk score of 10 is warranted due to B[a]P's role as the primary indicator for PAH toxicity. Its ability to cross biological barriers and form DNA adducts in humans, including in the placentas of smoking mothers, demonstrates its direct impact on human health. Its widespread occurrence in urban environments, persistent nature in soil and sediments, and its potential to facilitate viral replication (14) further solidify its status as a critical environmental and dietary toxin.

Polychlorinated Biphenyls (PCBs)
Risk Score: 10
Category: Environmental Contaminant (Persistent Organic Pollutant)

Health Impacts: Polychlorinated biphenyls (PCBs) and organochlorine pesticides like DDT and HCB are lipophilic chemicals that readily cross the placenta and bioconcentrate in breast milk. These contaminants are recognized neurodevelopmental toxicants; prenatal exposure is associated with neonatal hypotonia, hyporeflexia, and long-term decrements in IQ and executive function. Specifically, childhood studies indicate persistent deficits in attention, impulse control, and memory, particularly among children with high prenatal exposure. Beyond neurotoxicity, these substances are linked to intrauterine growth retardation and potential impairment of immune and thyroid functions (16).

Regulatory Status: Due to their extreme environmental persistence and toxicity, the production of PCBs and DDT was banned in the U.S. in the 1970s and in most industrialized nations over the following decade. Although environmental levels are generally declining, these compounds remain regulated under international agreements like the Stockholm Convention because they do not easily degrade (16).

Dose/Context Qualifiers: Non-occupational exposure occurs primarily through the consumption of contaminated animal fats, meat, dairy, and fatty fish, which accumulate these chemicals from the environment. Infants face a unique exposure profile: while they receive substantial doses via breastfeeding, research suggests that the nutritional benefits of nursing generally outweigh the risks of contaminant exposure (16). Notably, the impact of these toxins can be modified by co-exposures, such as methylmercury in maritime diets, and socio-environmental factors, where developmental "catch-up" is more likely in advantaged home environments.

Justification for Risk Score: A maximum risk score of 10 is justified by the proven ability of these organochlorines to induce permanent, multi-system damage during critical windows of

fetal development. Even at low levels of exposure typical of the general population, studies show measurable deficits in cognitive and behavioral health that can persist into adolescence (16). The combination of high bioaccumulation potential, global presence, and the lack of a clear safety threshold for neurodevelopmental effects makes these compounds a primary concern for population health.

Furan
Risk Score: 10
Category: Processing Contaminant (Thermal Degradation Product)

Health Impacts: Furan is a highly volatile heterocyclic compound primarily generated during thermal food processing via the Maillard reaction, carbohydrate degradation, and the oxidation of ascorbic acid or polyunsaturated fatty acids. Once ingested, it is bioactivated by the enzyme CYP2E1 into the reactive intermediate cis-2-butene-1,4-dial, which is known to bind with DNA and proteins. This metabolic process causes severe hepatotoxicity, characterized by hepatocellular necrosis and inflammation. Long-term animal studies demonstrate that chronic exposure leads to the development of hepatocellular adenomas and carcinomas, with the liver serving as the primary target organ due to its high metabolic activity (17).

Regulatory Status: Furan is currently classified as a Group 2B “possible human carcinogen” by the IARC and is “reasonably anticipated to be a human carcinogen” by the NTP. While no strict regulatory maximum limits have been established for food products, global agencies including the U.S. Food and Drug Association (FDA), the European Food Safety Authority (EFSA), and Food Standards Agency (FSA) actively maintain monitoring databases to estimate dietary exposure (17).

Dose/Context Qualifiers: Dietary exposure to furan is widespread but highly dependent on age and consumption habits. Coffee is the dominant source for adults, often accounting for 85% of total exposure, while jarred baby foods and canned products are primary concerns for infants and toddlers. Because Furan is exceptionally volatile (boiling point: 31°C), its concentration typically decreases when containers are opened or when food is reheated. However, its formation is complex and unavoidable in many heat-treated foods, leading to chronic low-dose exposure that closely approximates the levels where toxicological effects are observed in animal models (17).

Justification for Risk Score: A maximum risk score of 10 is warranted due to furan's confirmed status as a potent hepatocarcinogen that exhibits a clear dose-response relationship in multiple animal species. The compound is bioactivated into highly reactive metabolites, such as cis-2-butene-1,4-dial, which form protein and DNA adducts, leading to genotoxicity and irreversible cellular damage. Because furan is an inherent byproduct of thermal processing, human dietary exposure is considered chronic and largely unavoidable, occurring across a wide range of

common consumer goods. This widespread occurrence, combined with the extreme vulnerability of infants who consume high-heat processed jarred foods (17), underscores a significant public health risk that necessitates the highest level of concern.

Aspartame
Risk Score: 8
Category: Artificial Sweetener (High-Intensity Sweetener)

Health Impacts: Aspartame is a synthetic dipeptide that metabolizes into phenylalanine, aspartic acid, and methanol, the latter of which further breaks down into formaldehyde and formic acid. Research indicates these metabolites can trigger oxidative stress and lipid peroxidation, damaging cellular membranes and disrupting mitochondrial function. While recently classified by the IARC as a Group 2B "possibly carcinogenic" substance due to limited evidence of liver cancer, molecular studies suggest it may also impair antitumor immunity by exhausting T cells and promoting inflammatory pathways linked to tumor growth (18).

Regulatory Status: Despite ongoing debate, Aspartame is legal in the United States with an ADI of 50 mg/kg body weight and 40 mg/kg in the EU. It is approved for use in over 6,000 products globally, though it remains under continuous scientific review (18).

Dose/Context Qualifiers: The potential for adverse effects depends heavily on cumulative exposure, especially as aspartame is found in everything from diet sodas to pharmaceuticals. While typical consumption often falls below the ADI, concerns exist regarding chronic, low-level intake and high-exposure groups like children or heavy diet-soda consumers. Notably, research from the Ramazzini Institute suggests that prenatal exposure may be a critical window of vulnerability, with some animal models showing increased risks for lymphomas and leukemias at doses near current regulatory limits (18).

Justification for Risk Score: A score of 8 reflects the tension between widespread regulatory approval and evidence of significant molecular risk factors, including the production of formaldehyde, a known carcinogen. The score accounts for aspartame's ability to induce genomic instability and oxidative damage, balanced against the currently "limited" nature of direct human evidence for cancer (18). This high-priority score is reinforced by recent updates from health organizations suggesting moderated use and the substance's capacity to disrupt fundamental immune and metabolic pathways.

Butylated Hydroxyanisole (BHA)
Risk Score: 8
Category: Synthetic Antioxidant/Preservative

Health Impacts: Butylated hydroxyanisole (BHA) is an epigenetic (non-genotoxic) carcinogen that lacks direct DNA reactivity but promotes cancer through cellular irritation and oxidative stress. High-dose rodent studies consistently show BHA induces forestomach squamous cell carcinomas by driving abnormal cell proliferation (Kobets et al., 2022). Beyond its role as a "possible human carcinogen," it can act as a neoplasm promoter, enhancing the effects of other DNA-reactive toxins. It is also flagged for endocrine-disrupting activity and potential immunotoxicity (19).

Regulatory Status: BHA is Generally Recognized as Safe (GRAS) listed in the U.S. with specific concentration limits, though it is included on California's Proposition 65 list of known carcinogens. Internationally, the IARC and NTP recognize it as a possible or reasonably anticipated human carcinogen. While the EU permits its use, it imposes restrictions based on its classification as a Category 1 endocrine disruptor (19).

Dose/Context Qualifiers: Risk is highly dose-dependent, as epigenetic carcinogens typically exhibit a threshold (NOAEL) below which they do not cause cancer. Because human intake is significantly lower than the high concentrations required to cause rodent forestomach tumors, low-level dietary exposure is generally considered low risk. However, widespread use in processed foods, packaging, and cosmetics results in chronic, multi-route exposure for the general population (19).

Justification for Risk Score: A score of 8 is assigned due to BHA's consistent carcinogenicity in multiple species and its potency as a tumor promoter. While the human relevance of forestomach tumors is debated, the combination of its NTP and IARC classifications, documented endocrine disruption, and unavoidable dietary presence necessitates high-priority monitoring (19). The score reflects a balance between a clear biological threshold and the risks of chronic, cumulative exposure.

Titanium Dioxide (TiO_2, E171)
Risk Score: 8
Category: Whitening Agent/Color Additive/Opacifier

Health Impacts: Titanium dioxide (E171) contains a significant fraction of nanoparticles that, while poorly absorbed, have an exceptionally long half-life and accumulate in the body over time. The EFSA recently concluded that E171 is no longer safe due to evidence that it can induce DNA strand breaks and chromosomal damage (genotoxicity). Additionally, research suggests it may trigger inflammatory responses and the formation of aberrant crypt foci, which are recognized pre-neoplastic lesions in the colon (20).

Regulatory Status: E171 is banned in the European Union as a food additive as of 2022, following earlier bans in France. This decision was based on the inability to establish a safe daily intake level. Conversely, it remains permitted in the United States and several other regions, where regulatory bodies continue to review the emerging data on nanoparticle toxicity (20).

Dose/Context Qualifiers: Risk is highly dependent on the particle size and dispersion; nanoparticles (under 100 nm) are more likely to interact with cellular structures than larger particles. While internal exposure is low, the bioaccumulation in tissues means even small dietary amounts from candies, pastries, and supplements can build up over years. Children often face the highest relative exposure due to their body weight and high consumption of whitened confections (20).

Justification for Risk Score: A score of 8 reflects the EFSA's determination that a genotoxic risk cannot be ruled out, meaning no “safe” threshold can currently be defined. The score accounts for the confirmed biological accumulation of the particles and the potential for long-term colonic lesions, balanced against the lack of conclusive human cancer data. The significant global regulatory split and the vulnerability of high-consuming populations like children further solidify this high risk priority (20).

Propylparaben
Risk Score: 8
Category: Preservative (Antimicrobial Agent)

Health Impacts: Propyl paraben is a p-hydroxybenzoic acid ester that exerts weak estrogenic activity, as confirmed by estrogen receptor and uterotrophic assays. Research in post-weaning mammals shows that dietary exposure significantly impairs the male reproductive system. Specifically, propyl paraben causes a dose-dependent decrease in cauda epididymal sperm reserves and concentrations, as well as a significant reduction in daily sperm production and efficiency in the testes. Additionally, the compound adversely affects hormonal balance by causing a dose-dependent decrease in serum testosterone concentrations (21).

Regulatory Status: While the FDA designated propyl paraben as GRAS in 1977, this status is increasingly scrutinized due to the "GRAS loophole," which allows companies to bypass formal pre-market safety reviews. In contrast, the European Union banned propyl paraben in food in 2006 due to hormone disruption concerns. In the United States, regulatory action has shifted to the state level; the California Food Safety Act will ban the sale of food containing propyl paraben starting in January 2027 (22). Other jurisdictions, including Japan, currently maintain an ADI of 10 mg/kg body weight/day (21).

Dose/Context Qualifiers: Risk assessment focuses on the transition from weaning to maturity, where the reproductive system is highly sensitive. Studies using the AIN93G modified diet indicate that while organ weights (testes, prostates, and seminal vesicles) may remain unchanged, functional damage to sperm production occurs at doses as low as 0.10% of the diet. The most significant hormonal disruptions are observed at the highest tested dose of 1.00%, highlighting a clear dose-response relationship between intake and reproductive dysfunction (21).

Justification for Risk Score: A score of 8 is justified because propyl paraben induces measurable reproductive toxicity at doses directly relevant to current human regulatory limits (10 mg/kg bw/day). The evidence of endocrine-disrupting activity, specifically the suppression of testosterone and the reduction of sperm reserves, raises significant concerns for male fertility. Because the compound is utilized across multiple sectors including food, toiletries, and medicine, the risk score reflects the potential for chronic exposure to interfere with critical hormonal signaling pathways (21).

Red 40 (Allura Red AC, E129)
Risk Score: 7
Category: Synthetic Azo Dye/Artificial Food Color

Health Impacts: Red No. 40 (Allura Red AC) is a petroleum-derived naphthalene sulfonic acid that adds uniform color to products like gelatin, dairy, and alcoholic beverages (23). While the FDA and EFSA have historically deemed it safe, accumulating evidence suggests it acts as a behavioral trigger. The Southampton studies found that Red 40 mixtures significantly increase hyperactivity and irritability in children, regardless of whether they have an ADHD diagnosis (24). While it does not *cause* ADHD, it can exacerbate symptoms such as inattention and impulsiveness in susceptible individuals (23). Additionally, Red 40 can trigger hypersensitivity reactions (urticaria, asthma) and may contain trace contaminants like p-cresidine, a potential carcinogen (23, 24).

Regulatory Status: The FDA designated Red 40 as GRAS and most recently reviewed its safety in 2019, though it has not formally reevaluated the behavioral data in over a decade (23). The European Union already mandates a warning label stating the dye "may have an adverse effect on activity and attention in children" (24).

Dose/Context Qualifiers: Behavioral effects often emerge at doses (approx. 62 mg) that reflect typical daily consumption for U.S. children (24). Unlike natural dyes, Red 40 requires batch certification, where the FDA tests samples from every new production batch for purity. Because its purpose is purely cosmetic, families often use "elimination trials"—removing the dye for two weeks—to identify individual sensitivity (23).

Justification for Risk Score: A score of 7 is supported by replicated human evidence from double-blind, placebo-controlled trials showing a small but statistically significant impact on child behavior (effect size 0.12–0.28). This score reflects the dye's status as a public health concern rather than just an ADHD-specific one, as it affects children regardless of baseline hyperactivity levels (24).

Yellow 6 (Sunset Yellow FCF, E110)
Risk Score: 7
Category: Synthetic Azo Dye/Artificial Food Color

Health Impacts: Yellow 6 is one of the seven "FD&C" synthetic dyes approved for widespread use in the U.S. and is chemically categorized as an azo dye. Landmark epidemiological research, specifically the Southampton studies, identified Yellow 6 as a key component in color mixtures that increased hyperactivity, irritability, and inattention in children aged 3 and 8–9 years. These effects are not limited to children with a formal ADHD diagnosis; rather, AFCs like Yellow 6 are viewed as a public health problem that can "nudge" children across the diagnostic threshold by increasing symptom severity (24).

Regulatory Status: Yellow 6 is a certified color in the U.S., requiring the FDA to batch-test samples for purity. While the 2011 FDA Food Advisory Committee voted against a federal ban or warning label, the European Union requires all foods containing Yellow 6 (E110) to carry a mandatory warning: "may have an adverse effect on activity and attention in children" (24).

Dose/Context Qualifiers: The risk associated with Yellow 6 is compounded by its presence in a wide variety of pediatric-targeted foods, including beverages, gelatins, and snacks. Behavioral changes often occur at doses (approx. 62 mg) achievable through normal daily consumption (24). Significantly, EFSA concluded that sensitive individuals may experience allergic or hypersensitivity reactions even at dose levels within the established ADI (25).

Justification for Risk Score: A score of 7 reflects the replicated scientific evidence linking Yellow 6 to deleterious behavioral effects in the general pediatric population. The score accounts for the international regulatory tension, specifically the mandatory EU warning labels, and the potential for additive or synergistic effects when consumed alongside other synthetic dyes. While not a primary cause of ADHD, its role as a widespread environmental trigger for hyperactivity and its lack of functional utility in the food supply maintain its status as a high-priority risk (24).

Butylated Hydroxytoluene (BHT, E321)
Risk Score: 7
Category: Synthetic Antioxidant/Preservative

Health Impacts: BHT exhibits complex biological effects, primarily acting as a stabilizer to extend shelf life in products ranging from cereals to serums. While not classified as a human carcinogen, evidence from the ACGIH suggests it is a human respiratory irritant. Animal feeding studies reviewed by the Cosmetic Ingredient Review Expert Panel link BHT exposure to harm to the liver and kidneys, as well as the development of liver and lung tumors (26).

Regulatory Status: BHT has been designated as GRAS in the U.S. since 1959, allowing its use up to a maximum concentration of 0.02%. However, due to health concerns, states like Florida and Texas are currently including BHT in legislative proposals for bans, following the momentum created by the California Food Safety Act (26).

Dose/Context Qualifiers: BHT is utilized across multiple categories, including food packaging, cosmetics, and pharmaceuticals, leading to concerns over aggregate, long-term exposure (26).

Justification for Risk Score: A score of 7 reflects the demonstrated liver and kidney toxicity in animal models and its status as a respiratory and skin irritant. The score accounts for its potential role in tumor promotion and the increasing legislative pressure from U.S. states to ban the additive despite its decades-old GRAS status (26).

Acesulfame Potassium (Acesulfame-K, E950)
Risk Score: 7
Category: Artificial Sweetener (High-Intensity Sweetener)

Health Impacts: Acesulfame Potassium is a high-intensity, non-nutritive sweetener approximately 200 times sweeter than sugar. It is not biotransformed by the body; after oral administration, it is rapidly and completely absorbed and then excreted unchanged in the urine (approximately 98% within 24 hours in humans) with no evidence of bioaccumulation. While traditionally considered metabolically inert, recent scientific consensus suggests it may not be, with emerging evidence indicating potential effects on glucose homeostasis, sweet taste receptor signaling, and insulin secretion. Animal studies have also shown increased relative cecal weights and possible alterations in gut microbiota. Although initial rodent bioassays were negative for carcinogenicity, some studies in Swiss albino mice have observed dose-related increases in chromosomal aberrations (chromatid breaks) in bone marrow cells, though these results were not replicated in subsequent combination studies with aspartame (27).

Regulatory Status: Acesulfame-K is approved for use in both the United States and the European Union. The ADI is established at 15 mg/kg body weight. It is frequently used under trade names such as Sunette and Sweet One, often in combination with other sweeteners to achieve a synergistic taste profile and mask bitter aftertastes (27).

Dose/Context Qualifiers: Due to its stability at high temperatures (decomposition point of 225°C) and broad pH range, Acesulfame-K is used extensively in baked goods, dry powders, and carbonated beverages, leading to widespread human exposure. Because it is frequently co-consumed with other artificial sweeteners, attributing specific long-term health outcomes solely to Acesulfame-K is difficult. Modern research using genetically modified mouse models, such as the Tg.AC hemizygous and p53 haploinsufficient models, is ongoing to better understand its carcinogenic potential and mode of action in high-risk biological environments (27).

Justification for Risk Score: A score of 7 reflects the persistent scientific uncertainty stemming from early safety studies and emerging evidence that the compound may affect metabolic health and gut microbiome composition. While standard bioassays have not conclusively labeled it a carcinogen, the observation of genetic toxicity (chromosomal aberrations) in specific mouse models and its widespread, growing presence in the global food supply necessitate a cautious risk profile (27).

Sucralose (E955)
Risk Score: 7
Category: Artificial Sweetener (High-Intensity Sweetener)

Health Impacts: Sucralose, a chlorinated derivative of sucrose, was long deemed biologically inert; however, recent evidence indicates it is metabolically active. While only 16% is absorbed in the small intestine, it interacts extensively with T1R3 sweet taste receptors found in the gut, pancreas, and liver, triggering signaling pathways that can lead to hyperinsulinemia and altered glucose homeostasis. Chronic consumption is associated with gut microbiome dysbiosis, specifically decreasing beneficial bacteria like *Lactobacillus acidophilus* while increasing proinflammatory strains like *Proteobacteria* and *Ruminococcus*. Furthermore, studies link sucralose to liver damage, including hepatic fibrosis, Kupffer cell hyperplasia, and increased lipogenic activity via T1R3-mediated ROS production. Emerging research also highlights its ability to cross the placenta and enter breast milk, potentially inducing systemic inflammation in neonates (28).

Regulatory Status: Sucralose is approved by the FDA, even for children and adults with diabetes, with an ADI of 15 mg/kg body weight. Despite its “safe” classification by the WHO/FAO in 1998, a global alert was issued in 2023 concerning the potential links between sucralose consumption and systemic inflammation and metabolic diseases (28).

Dose/Context Qualifiers: Bioavailability varies significantly by age; children may exhibit plasma concentrations twice as high as adults due to lower glomerular filtration rates. While much of the compound is excreted in feces, recent findings show the presence of acetylated and glucuronide metabolites, with sucralose persisting in adipose tissue for up to two weeks post-ingestion. Its use in cooking is common, though its thermal stability is under scrutiny regarding the potential formation of toxic degradation products. Individual risk is heavily influenced by the presence of a “high-fat diet” co-exposure, which appears to amplify the sweetener's negative effects on insulin sensitivity (28).

Justification for Risk Score: A score of 7 is assigned due to the 2023 WHO alert and documented evidence of metabolic dysregulation, intestinal dysbiosis, and liver toxicity. While the FDA maintains its safety status, the transition of sucralose from an inert additive to a documented trigger for low-grade systemic inflammation and its ability to traverse the placental barrier justify a high-priority concern, particularly for pregnant women and developing children (28).

Neotame (E961)
Risk Score: 7
Category: Artificial Sweetener (High-Intensity Sweetener)

Health Impacts: Neotame is a highly potent artificial sweetener (7,000–13,000 times sweeter than sucrose) approved as safe due to its rapid metabolism and elimination. However, recent independent research has identified significant pathogenic effects on the gut. Neotame exposure causes intestinal epithelial cell apoptosis and death and disrupts the gut barrier by reducing the expression of the tight-junction molecule claudin-3, leading to increased monolayer leak. These damaging effects are mediated through the T1R3 sweet taste receptor pathway. Additionally, neotame alters the behavior of commensal bacteria like *E. coli* and *E. faecalis*, significantly increasing their biofilm formation and their capacity to adhere to and invade intestinal cells. Metabolites released by neotame-exposed *E. coli* have also been shown to directly reduce gut cell viability (29).

Regulatory Status: Approved approved by FDA in 2002 and EFSA in 2010. The ADI of Neotame is 2 mg/kg body weight per day which is no more than 10 mM per day in an individual with average weight (29).

Dose/Context Qualifiers: Neotame is used at very low concentrations, but even physiologically relevant doses (as low as 1 μM) can induce epithelial leak. Its impact is heavily influenced by the gut environment; in co-culture models, neotame exposure enhances the pathogenic profile of the microbiota, turning normally commensal bacteria into invasive threats (29).

Justification for Risk Score: A score of 7 is assigned based on evidence that neotame disrupts the intestinal barrier, induces cell death, and promotes microbial pathogenicity. While its absolute intake remains low, the discovery of T1R3-dependent toxicity and the sweetener's ability to drive dysbiosis and bacterial invasion represent a significant shift from its previous characterization as a biologically inert additive. The lack of long-term independent human data further justifies this high-priority concern (29).

Blue 2 (Indigotine, E132)
Risk Score: 7
Category: Synthetic Food Color (Indigoid Dye)

Health Impacts: Blue 2 is not considered safe by researchers due to a statistically significant increase in tumors, particularly brain gliomas, observed in male rats during high-quality chronic

toxicity studies. While most genotoxicity tests for this dye have been negative, one chromosomal aberration assay showed positive results. Although this report primarily focuses on traditional toxicology (organ damage and cancer) rather than neurobehavioral toxicity, it notes that mixtures of synthetic food dyes have been linked to hyperactivity and other impaired behaviors in children (30).

Regulatory Status: In the United States, Blue 2 was permanently listed for use in foods and ingested drugs in 1983. It is a certified color, meaning the FDA must test each batch to ensure it meets legal specifications for contaminants. In the European Union, a law passed by the European Parliament requires a warning notice on all foods containing certain dyes, including those tested in the "Southampton" studies, stating the product "may have an adverse effect on activity and attention in children" (30).

Dose/Context Qualifiers: The maximum ADI for Blue 2 is set at 2.5 mg/kg body weight per day, which is roughly 75 mg for a 30-kg child. Approximately 550,883 pounds of the dye were certified in 2009, accounting for 3.7% of all food dyes used—significantly less than Red 40, Yellow 5, or Yellow 6. Blue 2 is commonly found in beverages, candies, pet foods, and various drugs. Unlike many other dyes, Blue 2 is poorly absorbed; most is excreted in the feces, while the small amount that is absorbed is primarily excreted in urine (30).

Justification for Risk Score: A risk score of 7 is justified by the statistically significant incidence of brain gliomas in male rats, suggesting a potential carcinogenic risk that led researchers to conclude the dye should not be used in the food supply. This score also reflects concerns over behavioral impairments in children associated with dye mixtures, the positive finding in a genotoxicity study, and the regulatory requirement for warning labels in the European Union (30).

Green 3 (Fast Green FCF, E143)
Risk Score: 7
Category: Synthetic Food Color (Triarylmethane Dye)

Health Impacts: Green 3 is considered a suspect substance due to findings in high-dose chronic feeding studies involving rats. These studies revealed significant increases in urinary bladder transitional cell/urothelial neoplasms and testes Leydig's cell tumors (which are typically rare and benign in humans) in male rats. While it was not mutagenic in most assays, it yielded positive results in a Fischer rat embryo cell transformation assay, which is an indicator of carcinogenic potential. Despite these findings, the FDA pathologists concluded that the bladder and testes tumors were not treatment-related (30).

Regulatory Status: Green 3 is approved for use in the United States for food, drugs, and cosmetics (excluding the eye area), and it was permanently listed as a food coloring in 1982. It is one of the least-used dyes in the U.S. food supply. The British government advised companies to stop using most food dyes, and the European Union requires a warning label on most dye-containing foods (30).

Dose/Context Qualifiers: Human exposure to Green 3 is extremely low, with current production levels equivalent to only 0.1 mg/person/day. It represents only 0.1% of the total food dyes certified by the FDA in 2009. The dye is poorly absorbed, with approximately 94% excreted intact in feces. When used, it is typically found in beverages, candies, ice cream, sorbet, and dessert powders. The ADI is set at 2.5 mg/kg body weight per day (30).

Justification for Risk Score: A score of 7 reflects the significant increase in bladder and testes tumors in male rats, even though the FDA has dismissed these findings. The score also accounts for its positive results in a malignant cell transformation assay and the broader concerns regarding synthetic dyes being linked to hyperactivity and behavioral impairments in children. Given these toxicological considerations, researchers argue that Green 3 cannot be considered safe until further testing is conducted (30).

Propyl Gallate (E310)
Risk Score: 7
Category: Antioxidant/Preservative

Health Impacts: Propyl gallate is an antioxidant that raises significant safety concerns due to its potential endocrine-disrupting properties. Studies indicate it exhibits estrogenic activity by binding to estrogen receptors and inducing the transcription of estrogen-responsive genes. Animal models have demonstrated reproductive and developmental toxicity, and there is evidence that it can inhibit DNA polymerase, suggesting a potential for genotoxicity. Additionally, the compound is a known allergic sensitizer and has been linked to toxic effects in the liver and kidney when administered at high doses (31).

Regulatory Status: While propyl gallate is currently legal for use in both the United States and the European Union (where it is designated as E310), its status is under scrutiny. It is frequently used to prevent rancidity in fats, oils, and fat-containing processed foods, often in combination with other synthetic antioxidants like BHA and BHT. EFSA has explicitly noted data gaps regarding its endocrine-disrupting potential, maintaining its approval only while awaiting further safety data (31).

Dose/Context Qualifiers: The established ADI is 1.4 mg/kg body weight. Human exposure primarily occurs through the consumption of processed foods high in animal fats or vegetable oils. Because propyl gallate is often used alongside BHA and BHT, there is a risk of additive or synergistic toxic effects that are not typically captured in studies of the single additive. Individuals with diets heavy in preserved, fat-rich processed foods may reach or exceed the safety limits for this compound (31).

Justification for Risk Score: A risk score of 7 is assigned due to the additive's demonstrated estrogenic and reproductive toxicity, its potential for genotoxicity through DNA polymerase inhibition, and its role as an allergic sensitizer. The score also reflects significant regulatory uncertainty, highlighted by EFSA's identification of critical data gaps regarding endocrine disruption and the compound's widespread presence in the global food supply (31).

Carrageenan (E407)
Risk Score: 7
Category: Emulsifier/Thickener/Gelling Agent

Health Impacts: Carrageenan, a polysaccharide extracted from red algae, is classified into three types. kappa, iota, and lambda, all of which have been shown to induce inflammatory responses in animal models. While food-grade carrageenan is composed of high molecular weight molecules, it can be contaminated with or degraded into poligeenan (degraded carrageenan), a lower molecular weight form known to cause intestinal ulceration and lesions. Research indicates that carrageenan triggers the NF-κB inflammatory pathway and increases the production of reactive oxygen species (ROS), which can lead to intestinal epithelial cell death and increased barrier permeability. Furthermore, animal studies have linked its consumption to the exacerbation of colitis symptoms and the potential promotion of colonic tumors (32).

Regulatory Status: Food-grade carrageenan is currently approved as a food additive (E407) by both the FDA and the European Union. However, poligeenan is strictly prohibited as a food additive due to its high toxicity and association with colon cancer in animals. Due to concerns regarding the immature gastrointestinal systems of neonates, the use of carrageenan in infant formula is restricted in some regions (32).

Dose/Context Qualifiers: Widespread human exposure occurs through the consumption of processed foods, including dairy products, plant-based milks (such as soy and almond), processed meats, and confectionery. Scientific concern persists regarding the "degradation hypothesis," which suggests that the acidic environment of the human stomach or certain gut

bacteria may break down food-grade carrageenan into toxic poligeenan during digestion. Additionally, human clinical trials have shown that patients with Inflammatory Bowel Disease (IBD) in remission experience earlier relapses when consuming a diet containing carrageenan compared to a carrageenan-free diet (32).

Justification for Risk Score: A risk score of 7 is assigned due to the consistent ability of carrageenan to induce intestinal inflammation and epithelial damage in laboratory models. The score reflects the potential for *in vivo* degradation into carcinogenic poligeenan, the documented risk of relapse in IBD patients, and its role in disrupting the intestinal mucus barrier, which allows for increased bacterial translocation and systemic inflammation (32).

Polysorbate 80 (E433)
Risk Score: 7
Category: Emulsifier (Non-ionic Surfactant)

Health Impacts: Polysorbate 80 (P-80) significantly disrupts the symbiotic relationship between the host and the gut microbiota, promoting "low-grade" chronic inflammation. Research indicates that P-80 decreases the expression of Muc2 RNA, resulting in a thinner intestinal mucus layer that allows bacteria to reside closer to the epithelial cells. This breach of the gut barrier is associated with increased levels of pro-inflammatory markers such as fecal lipopolysaccharide (LPS) and flagellin. In animal models, chronic administration of P-80 led to obesity, impaired glycemic tolerance, and hyperinsulinemia, as well as liver-specific issues including larger mitochondria and altered liver enzymes (33).

Regulatory Status: While P-80 is currently approved for use by regulatory bodies like the FDA, it is one of the most widely used emulsifiers in the modern food industry. It is ubiquitous in highly processed items such as ice cream, margarine, and commercial baked goods, where it is used to provide a smooth, stable texture (33).

Dose/Context Qualifiers: The metabolic and inflammatory symptoms observed in studies resulted from P-80 concentrations modeled to reflect the cumulative intake of various emulsifiers in the human diet. Effects such as increased adiposity and liver dysfunction were noted following 12 weeks of exposure, suggesting that the risks are driven by chronic, long-term consumption. Furthermore, the impact of P-80 is mediated by the microbiota; for instance, P-80 fed mice showed an increase in Clostridium clusters and serum deoxycholic acid (DCA), a secondary bile acid linked to metabolic changes (33).

Justification for Risk Score: A risk score of 7 is assigned based on evidence that P-80 acts as a biological detergent that facilitates bacterial encroachment into the normally sterile mucus layer.

This disruption directly contributes to the development of metabolic syndrome and liver dysfunction. The score reflects the compound's ability to promote a pro-inflammatory microbiota and its widespread presence in ultra-processed foods, which ensures nearly constant exposure for the general population (33).

Polysorbate 60 (E435)
Risk Score: 7
Category: Emulsifier (Non-ionic Surfactant)

Health Impacts: Polysorbate 60 is a fatty acid ester of sorbitan that shares significant structural and functional similarities with Polysorbate 80, differing primarily in its fatty acid chain length (C18 for P-80 vs. C16 for P-60). Like other polysorbates, it can cause cell membrane perturbation and alter the gastrointestinal barrier. Research indicates that Polysorbate 60 can increase the permeability of intestinal markers; for example, in rat rectal perfusion studies, it caused a 1.5-fold increase in the absorption of sulfanilic acid. Furthermore, high-dose chronic exposure to polysorbates has been linked to hyperplasia, inflammation, and ulcers in the forestomach of mice, as well as an increased release of intracellular lysosomal enzymes, suggesting a potential to increase permeability to harmful compounds in the gut (34).

Regulatory Status: Polysorbate 60 is a widely used excipient and food additive approved in the United States and the European Union (E435). It is ubiquitous in the food supply, commonly found in baked goods, coffee creamers, and frozen desserts. In the pharmaceutical sector, it is present in thousands of licensed medicines and is used in topical, mucosal, oral, and injectable formulations (34).

Dose/Context Qualifiers: The impact of Polysorbate 60 is highly dependent on the luminal environment; its ability to alter the intestinal barrier is significantly amplified (up to 10-fold) in lipid-rich environments, such as when consumed with oils. Conversely, the presence of calcium in the luminal fluid may counteract these alterations. While human safety evaluations of up to 3 grams daily for 28 days did not show clinically recognizable adverse effects in healthy subjects, chronic high-dose consumption (10% to 20% w/v) in animal studies resulted in diarrhea due to an osmotic laxative effect (34).

Justification for Risk Score: A risk score of 7 is assigned based on the compound's demonstrated ability to perturb epithelial membranes and increase intestinal permeability. This score reflects the growing scientific consensus that non-ionic surfactants, including Polysorbate 60, can disrupt the intestinal mucus layer and promote low-grade inflammation by altering host-

microbiota interactions. The potential for Polysorbate 60 to facilitate the translocation of bacteria and harmful compounds across the gut barrier, combined with its widespread presence in ultra-processed foods, justifies its classification as a significant priority for those with inflammatory bowel conditions (34).

Polysorbate 65 (E436)
Risk Score: 7
Category: Emulsifier (Non-ionic Surfactant)

Health Impacts: Polysorbate 65, like its closely related counterpart Polysorbate 80, acts as a surfactant that can directly modify the intestinal mucus barrier. While Polysorbate 80 has been shown to increase the speed of *E. coli* within the mucus gel, potentially facilitating bacterial translocation, mechanistic studies of polysorbates as a group suggest they can lead to depletion of the mucus layer and structural alterations in the mucus gel. These "detergent-like" properties may cause mucosal components to slough off, reducing the protective thickness of the barrier that normally keeps microbes at a safe distance from the epithelial cells. Chronic exposure to such emulsifiers is associated with an increased prevalence of metabolic syndrome and inflammatory bowel diseases (35).

Regulatory Status: Polysorbate 65 is approved for use in the United States and the European Union. While it is used less frequently than Polysorbate 80 or 60, it remains a common ingredient in specific food categories such as frozen desserts, baked goods, and whipped toppings due to its effective emulsification properties (35).

Dose/Context Qualifiers: Dietary exposure to Polysorbate 65 occurs primarily through processed foods, with an established group ADI of 25 mg/kg body weight for polysorbates. Research indicates that even acute exposure to these emulsifiers can impact mucus barrier properties, though the final concentration in the gut is often diluted by other food matrix contents. Individual susceptibility is likely influenced by the baseline microbiome composition, as emulsifiers have been shown to reduce microbial diversity and increase the presence of "mucolytic" (mucus-eating) bacteria like *Ruminococcus gnavus* (35).

Justification for Risk Score: A risk score of 7 is assigned based on the demonstrated ability of polysorbate surfactants to compromise intestinal mucus integrity and modulate the transport of pathogens like *E. coli*. The score reflects the strong mechanistic evidence linking food emulsifiers to intestinal inflammation, the potential for increased bacterial encroachment on the epithelium, and the lack of extensive, compound-specific safety data for Polysorbate 65 despite its widespread presence in the food supply (35).

Sodium Benzoate + Ascorbic Acid (Combined Exposure)
Risk Score: 7
Category: Preservative System (Context-Dependent Carcinogen Formation)

Health Impacts: Sodium benzoate is a common food chemical used to preserve fruit juices, sauces, and syrups, but it has been linked to significant health concerns, including hormone disruption, reduced fertility, and DNA damage. Of particular concern is its potential to form benzene, a chemical associated with blood cancers. This carcinogenic reaction occurs specifically when sodium benzoate is combined with ascorbic acid (vitamin C) or citric acid and exposed to elevated temperatures or sunlight (36)

Regulatory Status: Sodium benzoate is currently legal for use in food under the FDA's GRAS loophole. This regulation allows manufacturers to self-certify the safety of their ingredients without direct FDA approval. Critics argue this is an outdated system, as nearly 99% of new food chemicals added since 2000 have bypassed federal oversight using this method. Furthermore, current regulations often evaluate chemicals individually rather than addressing the toxic combinations, such as benzoate mixed with vitamin C, found in over 20,000 products (36).

Dose/Context Qualifiers: The risk of benzene formation is highest in products that stabilize large amounts of the preservative in the presence of acidic agents. Common items likely to contain this hazardous combination include sodas, salad dressings, sauces, and cakes. Exposure can be mitigated by choosing certified organic products, which must adhere to stricter standards regarding artificial additives, and by reducing the intake of ultra-processed foods (36).

Justification for Risk Score: A score of 7 is assigned because sodium benzoate can reliably form benzene (a known human carcinogen) when mixed with common acids under predictable storage conditions like heat or light. This risk is compounded by the chemical's widespread presence in the food supply and a regulatory environment that fails to account for the cumulative harm of combined ingredients. The inability of consumers to know if benzene has formed in a specific product before consumption creates a significant safety concern (36).

High Fructose Corn Syrup (HFCS)
Risk Score: 7
Category: Nutritive Sweetener/Caloric Sweetener

Health Impacts: Excessive intake of High Fructose Corn Syrup (HFCS) is a primary driver of Impaired Glucose Tolerance (IGT) and Type 2 Diabetes (T2D). Research indicates that HFCS disrupts glucose and fructose metabolism by significantly decreasing the expression of key metabolic regulators in the pancreas, including Glut2 (glucose transporter 2), glucokinase (Gck), and ketohexokinase (Khk). Unlike obesity-driven diabetes, HFCS can induce a "non-obese" diabetic state characterized by a specific insulin-secretion defect rather than insulin resistance. Furthermore, excessive HFCS consumption reduces the expression of Pdx1, a critical transcription factor for insulin secretion and β-cell replication, and lowers pancreatic amylase levels, a known marker of pancreatic dysfunction (37).

Regulatory Status: HFCS was developed in the 1960s as a liquid alternative to sucrose and was rapidly adopted by the food and beverage industry in the 1970s due to its low cost and high sweetness. It holds GRAS status in the United States. While some scientific reviews debate its direct role in the obesity epidemic, recent controlled studies highlight its potential to induce metabolic disorders even in the absence of weight gain when caloric intake is otherwise balanced (37).

Dose/Context Qualifiers: The metabolic impact of HFCS is heavily influenced by the overall nutritional balance of the diet. In contexts where HFCS-rich beverages (like soft drinks) replace proper nutrition, metabolic harm occurs through a significant nutrient imbalance—specifically, a high ingestion rate of carbohydrates (up to 78% of total calories) coupled with a low intake of proteins and fats. While excessive caloric intake combined with HFCS leads to obesity and adipose tissue hypertrophy, HFCS consumption *alone* (under controlled calories) primarily targets pancreatic endocrine and exocrine function, leading to decreased levels of the anti-inflammatory cytokine adiponectin (37).

Justification for Risk Score: A risk score of 7 is assigned due to HFCS's demonstrated ability to cause pancreatic dysfunction and impaired glucose tolerance independent of weight gain. This reflects the compound's capacity to induce "metabolically unhealthy normal weight" states, where individuals develop T2D despite having a normal BMI. The score is further justified by the significant downregulation of vital metabolic enzymes (Gck, Khk, Glut2) and the long-term risk of insulin-secretion failure associated with chronic, high-percentage carbohydrate intake from HFCS-sweetened beverages (37).

Sulfites (All Forms: E220-E228)
Risk Score: 7 (General Population); Risk Amplified to 9+ for Asthmatic Individuals
Category: Preservative/Antioxidant

Forms: Sulfur dioxide (E220), sodium sulfite (E221), sodium bisulfite (E222), sodium metabisulfite (E223), potassium metabisulfite (E224), calcium sulfite (E226), calcium bisulfite (E227), potassium bisulfite (E228)

Health Impacts: Red 40 is a petroleum-derived dye linked to significant behavioral and physiological concerns. It is a primary trigger for hypersensitivity and hyperactivity in children, contributing to ADHD-like symptoms. While it is one of the most widely used dyes, it contains carcinogenic contaminants such as p-Cresidine, which is "reasonably anticipated to be a human carcinogen". Animal studies have also noted the potential for Red 40 to accelerate the appearance of immune-system tumors (reticuloendothelial tumors) in mice, though the FDA considered these findings statistically insignificant (38).

Regulatory Status: Red 40 is approved by the FDA and the EU, though the EU requires a warning label on most dyed foods stating they "may have an adverse effect on activity and attention in children". In the U.S., it remains legal without such warnings despite repeated petitions from consumer advocacy groups to ban it due to its lack of nutritional benefit and associated risks (38).

Dose/Context Qualifiers: As the most consumed food dye in the U.S., Red 40 is found in thousands of products, including sodas, candies, breakfast cereals, gelatin desserts, and even some medications. Because it is used primarily for aesthetic purposes in ultra-processed foods, exposure is often chronic. Children are particularly vulnerable because they consume more dye per pound of body weight than adults (38).

Justification for Risk Score: A score of 7 reflects the documented impact on child behavior, the presence of carcinogenic contaminants, and the high frequency of population exposure. While the evidence for direct human carcinogenicity is debated by regulators, the combination of behavioral disruption and the availability of safer natural alternatives justifies a high risk rating for a purely cosmetic additive (38).

Sodium Nitrite/Nitrate (E249-E252)
Risk Score: 7
Category: Preservative/Curing Agent/Color Fixative

Health Impacts: The primary health concern regarding nitrites and nitrates is their conversion into N-nitroso compounds (NOCs), such as N-Nitrosodimethylamine (NDMA). These compounds are formed through the nitrosation of amines and amides, a process accelerated by the acidic environment of the stomach or high-heat cooking. NOCs are potent carcinogens and genotoxic agents that can cause direct DNA damage. Due to these mechanisms, the International Agency for Research on Cancer (IARC) classifies processed meats (cured, salted, or smoked) as Group 1: Carcinogenic to humans, specifically linking their consumption to colorectal cancer (CRC). Additionally, nitrites pose an acute risk of methemoglobinemia (Blue Baby Syndrome) in infants by reducing the oxygen-carrying capacity of the blood (39).

Regulatory Status: Nitrites are considered "indispensable" in the current meat industry because they perform multiple functions that cannot yet be fully replicated by a single alternative. Most countries establish strict limits on residual nitrite (typically 150–200 ppm) to balance safety with the prevention of botulism—a deadly paralytic illness caused by *Clostridium botulinum* (39).

Dose/Context Qualifiers: Fried and grilled meats often have poorly monitored residual nitrite levels and higher NOC formation due to heat. The production of NOCs can be inhibited by the presence of Vitamins C and E, which are often added to cured meats to mitigate risk. While meat accounts for only ~5% of total nitrite exposure (with vegetables and water providing the rest), the specific combination of nitrites with meat proteins (amines) makes processed meat a unique carcinogenic risk (39).

Justification for Risk Score: A score of 7 is assigned because nitrites are a key mechanistic factor in the IARC's Group 1 classification of processed meats as known human carcinogens. The score reflects the strong epidemiological link to colorectal cancer, the potential for genotoxic DNA damage, and the fact that residual levels in popular products (like fried meats) are often inconsistent (39). Despite their role in preventing botulism, the widespread chronic exposure through processed diets justifies significant safety concern.

Monosodium Glutamate (MSG, E621)
Risk Score: 6
Category: Flavor Enhancer (Umami Taste)

Health Impacts: MSG is the sodium salt of glutamic acid, a common amino acid found naturally in the body and in foods like tomatoes and cheese. While widely used as a flavor enhancer, it is associated with "MSG symptom complex"—a set of mild, temporary symptoms including flushing, headaches, muscle aches, numbness or burning around the mouth, and heart palpitations. While anecdotal reports of "Chinese restaurant syndrome" have existed since 1968, clinical studies have failed to establish a conclusive link between the additive and these symptoms (40).

Regulatory Status: The FDA rates MSG as GRAS An FDA-commissioned study found no evidence that MSG in food causes the reported symptoms under normal conditions. Although there are no specific medical tests to diagnose MSG sensitivity, the additive remains legal globally and is common in various cuisines (40).

Dose/Context Qualifiers: Risk is highly dependent on the amount consumed and the presence of other food. Minor reactions were only observed in individuals who consumed 3 grams or more of MSG alone on an empty stomach. For context, most foods containing MSG provide less than 0.5 grams, making the reported adverse reactions unlikely during standard dietary habits (40).

Justification for Risk Score: A score of 6 reflects the persistence of acute sensitivity reports (flushing, tingling, and drowsiness) in a subset of the population, balanced against the lack of clinical evidence linking standard dietary intake to long-term health problems. While the symptoms are generally mild and self-resolving, the potential for rare, serious allergic-type reactions, such as shortness of breath or swelling of the throat, requires medical caution (40).

Yellow 5 (Tartrazine, E102)
Risk Score: 6
Category: Synthetic Azo Dye/Artificial Food Color

Health Impacts: Yellow 5 is a petroleum-derived azo dye that is the second most widely used food coloring. While not found to be carcinogenic in rats, it has not been adequately tested in mice, and 6 out of 11 genotoxicity studies, including comet and cytogenetics assays, showed positive results for DNA or chromosomal damage. It is well-documented to cause hypersensitivity reactions, sometimes severe, including urticaria (hives), asthma, angioedema (swelling), palpitations, and blurred vision. Clinical studies indicate a strong association with aspirin-intolerance, with reactions occurring in 20% of aspirin-intolerant patients. Additionally, Yellow 5 has been identified as a trigger for hyperactivity and other behavioral impairments in children (30).

Regulatory Status: In the United States, Yellow 5 is legal but requires batch-by-batch FDA certification to ensure contaminants like lead and benzidine do not exceed legal limits. However, the European Union mandates a warning notice on dye-containing foods stating they "may have an adverse effect on activity and attention in children". British authorities have also advised the food industry to eliminate the dye entirely. The FDA currently sets the ADI at 5 mg/kg/day (30).

Dose/Context Qualifiers: Widespread exposure occurs through bakery goods, beverages, candies, and pharmaceuticals, with U.S. production equivalent to 15 mg per person daily. Many children consume several times this average. The dye is often contaminated with carcinogenic impurities like benzidine and 4-aminobiphenyl. While the FDA limits "free" benzidine, research shows that "bound" benzidine, which can be up to 83 ppb in some batches, is liberated in the gastrointestinal tract and is not currently measured during standard certification (30).

Justification for Risk Score: A score of 6 is justified by the dye's significant genotoxic potential and its role in triggering behavioral issues in children, which prompted mandatory EU warning labels. The risk is further elevated by documented severe allergic reactions, cross-reactivity with aspirin, and the presence of carcinogenic contaminants (like benzidine) that may exceed safe thresholds due to current testing limitations regarding bound forms (30).

Blue 1 (Brilliant Blue FCF, E133)
Risk Score: 6
Category: Synthetic Triarylmethane Dye/Artificial Food Color

Health Impacts: Blue 1 is a petroleum-derived dye that raises specific neurotoxicity concerns due to its potential impact on brain development. While the dye is poorly absorbed by the gastrointestinal tract, preliminary *in vitro* studies found that Blue 1 inhibits neurite growth and acts synergistically with L-glutamic acid (a relative of MSG) to impair neuronal development. These effects are particularly worrisome for fetuses and infants under six months old, as their blood-brain barrier is not fully developed. Although key industry-sponsored studies did not find carcinogenicity in rats or mice, an unpublished study reported a statistically significant increase in kidney tumors in male mice. Additionally, the dye can cause hypersensitivity (allergic) reactions (30).

Regulatory Status: Blue 1 received FDA approval for general food use in 1969. While the FDA suggests a maximum ADI of 12 mg/kg bw/day, the European Union requires a warning notice on dye-containing foods stating they "may have an adverse effect on activity and attention in children". British authorities have also advised companies to eliminate most food dyes, including those tested in mixtures that showed behavioral impairment in children (30).

Dose/Context Qualifiers: Blue 1 is widely used in baked goods, beverages, candies, and cereals. Current average production is approximately 3 mg per person per day across the general population. For a 30-kg child, the ADI equates to 360 mg/day, a level that some "high users" may approach given that children consume more dyes per unit of body weight than adults. Because the dye is chemically almost identical to Green 3, there are concerns regarding its potential for similar biological activity (30).

Justification for Risk Score: A score of 6 reflects the dye's potential neurotoxicity and its synergy with other food additives, as well as the unresolved significance of kidney tumors observed in unpublished animal research. While most industry studies are negative for carcinogenicity, the requirement for EU warning labels due to behavioral concerns and the vulnerability of infants with incomplete blood-brain barriers justify a heightened risk assessment (30).

Propylene Glycol Alginate (E405)
Risk Score: 6
Category: Emulsifier/Thickener/Stabilizer

Health Impacts: Propylene glycol alginate is metabolized into alginic acid and propylene glycol. While low-level oral exposure is generally considered safe, high doses can lead to metabolic acidosis and an increased osmolal gap as the substance is converted into lactic and pyruvic acids. In clinical cases of acute poisoning, neurotoxic effects including stupor, repetitive convulsions, and mental depression have been documented. At extreme acute doses (e.g., 23,500 mg/kg in rats), serious systemic issues such as hemorrhagic enteritis and lymphocyte depletion can occur (41).

Regulatory Status: The FDA classifies propylene glycol as GRAS for use as a direct food additive and in flavorings, drugs, and cosmetics. While the federal government has developed regulations and guidelines to protect the public from potential adverse health effects, it is not routinely tested for unless specific exposure can be linked to "bad symptoms" (42).

Dose/Context Qualifiers: According to the WHO, the ADI is established at 25 mg of propylene glycol for every kilogram of body weight. While exposure through food, cosmetics, or medicine is not generally considered harmful, more intense exposure can occur in enclosed spaces where the substance is used to create artificial smoke or mists, such as in theatrical performances, rock concerts, or fire-fighting training. Propylene glycol is highly soluble, mixing completely with water and soaking into soil, and it can also migrate from certain types of food packaging into the food itself. Once in the body, it typically breaks down within 48 hours, making it difficult to detect through medical testing (42).

Justification for Risk Score: A score of 6 reflects the documented potential for neurotoxicity, metabolic acidosis, and red blood cell hemolysis at high exposure levels (41). While it is considered generally safe, studies of both humans and animals indicate that repeated oral, nasal, skin, or eye exposure for even a short time can cause irritation. Additionally, its ability to enter the bloodstream through inhalation of mists or direct skin contact (if not washed off) increases the risk of systemic exposure beyond simple ingestion. The score also reflects the potential for more concentrated exposure in specific professional or recreational settings and the fact that it is difficult to detect through routine medical testing (42).

Sodium Saccharin (E954)
Risk Score: 6
Category: Artificial Sweetener (High-Intensity Sweetener)

Health Impacts: Sodium saccharin has been extensively studied for its carcinogenic potential, specifically regarding its ability to induce bladder tumors in male rats. Research indicates that these tumors result from a non-genotoxic, species-specific mechanism involving high doses that lead to the formation of a calcium phosphate-containing precipitate in the urine, causing chronic irritation and regenerative cell proliferation in the bladder lining. However, this physiological response is considered not relevant to humans due to fundamental differences in urinary chemistry. While high-dose studies in male rats showed increased tumor incidence, extensive epidemiological data, including large-scale case-control studies, have found no consistent evidence that saccharin consumption increases the risk of bladder cancer in humans (43).

Regulatory Status: Saccharin is legal for use in the United States and globally. In 2000, the National Toxicology Program (NTP) officially delisted saccharin from its *Report on Carcinogens*, and it was subsequently removed from California's Proposition 65 list in 2001 after it was determined that the rat-specific mechanism did not pose a human cancer risk. The International Agency for Research on Cancer (IARC) has reclassified saccharin from Group 2B to Group 3 (not classifiable as to its carcinogenicity to humans). The established ADI remains at 5 mg/kg body weight (43).

Dose/Context Qualifiers: The induction of bladder tumors is dependent on a combination of high salt intake and specific urinary proteins found in male rats but not in humans. Typical human consumption levels are significantly lower than the doses used in rodent bioassays that produced tumors. Public perception of saccharin remains influenced by the original 1970s findings, which necessitated warning labels until the scientific consensus on its safety was updated in 2000 (43).

Justification for Risk Score: A score of 6 reflects saccharin's complex history as a former "known carcinogen," which continues to drive public concern despite current scientific evidence. The score accounts for the confirmed tumorigenic activity in male rats across multiple generations, which requires detailed mechanistic explanation to distinguish from human risk. While the risk is moderated by the lack of human epidemiological evidence and the determination that the rodent mechanism is non-relevant, the score remains at 6 due to its widespread exposure in diet products and pharmaceuticals, as well as the ongoing scientific debate regarding high-dose physiological impacts (43).

Phosphoric Acid/Phosphate Additives (E338-E341)
Risk Score: 6 (General Population); Risk Amplified to 8+ for Chronic Kidney Disease Patients
Category: Acidulant/Buffering Agent/Sequestrant

Health Impacts: Inorganic phosphate additives are highly problematic because they are nearly 100% bioavailable, unlike organic phosphorus found naturally in whole foods, which has an absorption rate of only 40–60%. Excessive intake of these additives leads to secondary hyperparathyroidism and bone mineral loss as the body attempts to balance phosphorus. High serum phosphate levels are associated with vascular calcification, arterial stiffness, and increased cardiovascular mortality. For patients with Chronic Kidney Disease (CKD), the inability to stop this excess phosphorus results in severe systemic damage and increased mortality risk (44).

Regulatory Status: Phosphate additives are legally permitted in the United States and the European Union, often lacking specific dietary limits despite emerging health evidence. Current food labeling regulations are a major hurdle for public health; they do not require manufacturers to list the amount of phosphorus on nutrition facts panels, nor do they distinguish between low-bioavailability organic sources and high-bioavailability inorganic additives. While clinical guidelines like those from Kidney Disease: Improving Global Outcomes (KDIGO) strongly recommend limiting these additives for kidney patients, the lack of transparency in labeling makes informed consumer choices nearly impossible (44).

Dose/Context Qualifiers: Population-wide exposure has surged as phosphates are now standard in ultra-processed foods, including processed meats, baked goods, and fast food. A single serving of processed cheese can contain between 300–450 mg of highly bioavailable phosphorus, while a typical cola serving adds 40–70 mg of phosphoric acid. While individuals with normal kidney function may initially tolerate moderate excess, chronic high intake contributes to “vascular aging”. For those with any stage of kidney impairment, even moderate dietary phosphate poses an immediate and severe health risk (44).

Justification for Risk Score: A score of 6 for the general population is justified by the nearly complete bioavailability of inorganic phosphates, which creates a disproportionate mineral burden leading to vascular and bone demineralization over time. This risk is compounded by the dramatic rise in exposure through ultra-processed foods and the systemic failure of labeling laws to identify these hidden additives (44). For CKD patients, the score increases to 8–9 because hyperphosphatemia is a direct driver of cardiovascular events and mortality in this population, making the widespread use of these additives a critical medical hazard.

Yeast Extract
Risk Score: 6
Category: Flavor Enhancer (Natural Glutamate Source)

Health Impacts: Yeast extract is a safe and nutritious natural product that supplies essential dietary nutrients, including vitamins, minerals, and proteins with an essential amino acid profile that meets international standards for healthy foods. It contains flavor-enhancing amino acids like glutamic acid, which ranges from 500 to 17,500 mg per 100g, and provides high antioxidant capacity, measured at ten times that of blueberries, due to its polysaccharide and phenolic content. While it offers benefits such as enhancing human immunity and reducing liver lipids, its primary health risk involves a high nucleic acid content (up to 15%) that is ten times higher than human tissues. Excessive intake of these nucleic acids can increase uric acid levels, potentially leading to hyperuricemia and gout, prompting recommendations to limit daily intake to 2 grams for adults (45).

Regulatory Status: Yeast extract, also known as "yeast hydrolysate" in the food industry, is regarded as GRAS by most food safety certification bodies worldwide. It is increasingly valued as a high-quality, natural alternative to synthetic additives, fitting the rising consumer demand for healthy and safe food products (45).

Dose/Context Qualifiers: Commonly used to enhance the flavor of soups, sauces, and savory snacks, yeast extract typically functions as the fourth most important natural flavoring agent globally. It contains nucleotides like AMP, IMP, and GMP that are 100 times more taste-active than seasonings such as monosodium glutamate, making it highly effective even in small concentrations. Beyond flavoring, it is used in animal feed as an antibiotic substitute and in biotechnology as a nutrient-rich growth medium for microbial fermentation. Sodium content in yeast extract varies significantly based on the production process, ranging from 1.0 to 1,356.3 mg per 100g (45).

Justification for Risk Score: The safety profile of yeast extract is characterized by its dual nature as a nutrient-dense supplement and a source of specific health risks, particularly regarding its high purine and nucleic acid levels. While it provides significant antioxidant and anti-inflammatory benefits, its widespread use in processed foods means consumers may face excessive nucleic acid exposure if intake is not monitored. Additionally, the presence of bitter compounds from hops in waste brewer's yeast requires specialized debittering processes to ensure consumer acceptance. The potential for undesirable "yeast tastes" or odors from excessive heat treatment further necessitates careful industrial processing to maintain its status as a high-quality natural ingredient (45).

Disodium Inosinate (E631) and Disodium Guanylate (E627)
Risk Score: 5
Category: Flavor Enhancers (Nucleotide-Based Umami Enhancers)

Health Impacts: Disodium guanylate is a flavor enhancer that works synergistically with MSG to create "umami," a savory or meaty taste. Humans respond to mixtures of MSG and nucleotides like disodium guanylate eight times more strongly than to MSG alone, allowing for a reduction in total salt intake. However, because guanylates are metabolized into purines, compounds that can raise uric acid levels in the body, consumption may be problematic for specific groups. While generally regarded as safe, it can contribute to oxidative stress and inflammation based on animal studies, and those with MSG sensitivity may experience headaches, muscle tightness, or flushing when consuming it in combination with glutamates (46).

Regulatory Status: Disodium guanylate is considered safe by both the FDA in the United States and the EFSA. Despite this classification, specific dosage guidelines or "adequate intake" levels have not been established due to a lack of comprehensive research (46).

Dose/Context Qualifiers: While disodium guanylate occurs naturally in foods like fish and dried shiitake mushrooms (which contain 150 mg per 100 grams), it is most commonly encountered as an additive in processed goods such as canned soups, potato chips, instant noodles, and spice blends. It is typically used in small, varying amounts to amplify the intensity of salt. Because of its metabolism into purines, avoidance is specifically recommended for individuals with gout or a history of uric acid kidney stones. Furthermore, because it is almost always paired with MSG, those with MSG sensitivities must be cautious of products containing this additive (46).

Justification for Risk Score: A moderate risk score of 5 is justified by the lack of established safety limits and the potential for disodium guanylate to increase uric acid levels, posing a direct risk to those with gout or kidney stones. The score also reflects the additive's role in amplifying the effects of MSG, which can trigger reactions in sensitive individuals. Additionally, the practice of labeling the compound under vague terms like "natural flavors" or "yeast extract" can make it difficult for concerned consumers to identify and avoid, while its presence in a wide array of processed foods ensures frequent dietary exposure (46).

Dextrose (as Additive)
Risk Score: 5
Category: Nutritive Sweetener/Bulking Agent

Health Impacts: Dextrose is a sugar typically derived from corn or wheat that is nearly identical to the glucose found in the human bloodstream, allowing the body to use it almost immediately for energy. Because it has a high glycemic index, it causes a rapid increase in blood sugar levels, which can be beneficial for replenishing energy after intense exercise or aiding mental focus. However, excessive consumption carries significant risks, including weight gain and obesity, as the body quickly stores unused sugar as fat. Long-term overconsumption is linked to serious conditions such as heart disease, kidney disease, liver disease, and type 2 diabetes. Furthermore, regular intake can lead to insulin resistance, which causes fatigue and increases the risk of various chronic illnesses (47).

Regulatory Status: In the medical and pharmaceutical sectors, Dextrose is regulated as a drug product; for instance, the FDA has approved dextrose concentrations of 20g/100mL and 50g/100mL in plastic containers as safe and effective for parenteral nutrition (intravenous feeding). These high-concentration versions are indicated as a source of calories for patients who cannot receive nutrition orally or enterally (48).

Dose/Context Qualifiers: The impact of dextrose is highly dependent on the consumer's health status and the quantity ingested. For bodybuilders or those facing mental exertion, it serves as a fast-acting energy source; for people with diabetes, dextrose tablets are a critical tool for managing low blood sugar episodes. The high glycemic nature of dextrose makes it dangerous for those with existing diabetes, heart disease, or kidney problems, as it puts a strain on the organs and can cause complications like frequent urination, nausea, and stomach pain (47).

Justification for Risk Score: Dextrose is given a score of 5 because its effects are primarily determined by consumption patterns rather than inherent toxicity. While it is a natural source of energy similar to blood sugar, its ability to cause rapid spikes in glucose makes it a significant risk factor for insulin resistance and organ damage when eaten in excess. The risk is further heightened for specific vulnerable populations, such as those with corn allergies, pulmonary edema, or low potassium levels. While it is useful for specific energy needs and medical applications, its presence in a wide variety of processed foods contributes to long-term health issues like fatty liver buildup and heart disease (47).

Calcium Propionate (E282)
Risk Score: 5
Category: Preservative (Antimicrobial Agent)

Health Impacts: Calcium propionate is generally well-tolerated by most people, but research indicates it may trigger adverse reactions in specific individuals. In a study of 27 children, daily consumption of bread containing the additive was linked to irritability, restlessness, poor attention, and sleep disturbances, though the body naturally produces similar propionates during fiber fermentation which complicates the assessment of these effects. Additionally, some research suggests that propionate intake might stimulate the release of insulin and glucagon, potentially leading to insulin resistance and an increased risk of type 2 diabetes. While rare side effects like headaches and migraines have been reported, the substance is not stored in the body; instead, it is broken down by the digestive tract, absorbed, and readily eliminated (49).

Regulatory Status: Extensively studied by major health organizations, calcium propionate is approved for use by the FDA, which classifies it as "generally recognized as safe." Because it is considered a very low-risk additive, the WHO and the Food and Agriculture Organization (FAO) have not even established a specific limit for ADI. It is a common preservation tool in the global food industry, identified as E282, and is used to extend the shelf life of diverse products including breads, dairy, processed meats, and even alcoholic beverages by interfering with the reproduction of mold and bacteria (49).

Dose/Context Qualifiers: It's estimated that a typical person consumes only 0.23 mg/kg body weight per day. Animal studies have shown that significantly higher doses—up to 4% of a total diet—resulted in no toxic effects over a year, suggesting that the standard human dose is well within safety margins for the general population (49).

Justification for Risk Score: A risk score of 5 reflects a balance between the additive's documented safety record and specific concerns regarding pediatric behavior and metabolic health. The score accounts for evidence from controlled trials showing irritability and sleep issues in children, as well as potential links to insulin resistance, which are particularly relevant given how widespread the additive is in common staples like bread. While these factors suggest a need for caution among sensitive groups, the score is moderated by the fact that the FDA and WHO consider it very low risk, it does not bioaccumulate in human cells, and it is a substance that the human microbiome produces naturally (49).

Advantame (E969)
Risk Score: 5
Category: Artificial Sweetener (High-Intensity Sweetener)

Health Impacts: Advantame is a non-nutritive sweetener and an N-substituted derivative of aspartame that is structurally similar to neotame. Unlike aspartame, it cannot form diketopiperazine derivatives because it lacks a free amino group for cyclization. To establish its safety, the FDA evaluated 37 studies covering immune, reproductive, and nervous system effects, as well as carcinogenicity. Additionally, it has been shown not to affect glucose homeostasis, making it a suitable alternative for individuals with Type II diabetes. While it is a derivative of aspartame, its extreme potency means it is used at much lower levels; however, it does undergo hydrolysis, with its major degradation product being advantame-acid (50).

Regulatory Status: Advantame was approved as a general-purpose sweetener and flavor enhancer by the FDA in 2014. It is also permitted in Australia and New Zealand under Good Manufacturing Practices (GMP) and has been assigned INS No. 969 by the Codex Committee on Food Additives. While the FDA established its safety through extensive review, FAO/WHO Joint Expert Committee on Food Additives (JECFA) published tentative specifications in 2013, requesting further data on analytical methods for certain catalysts like palladium and platinum. In the European Union, it is designated as E969 (50).

Dose/Context Qualifiers: Advantame is exceptionally potent, measuring approximately 20,000 to 37,000 times sweeter than sucrose depending on the food matrix. Because of this, it is used in minuscule amounts, often at parts-per-million levels, which results in an estimated daily intake (EDI) of roughly 1.26 mg/kg body weight. It is heat-stable and suitable for baking, though it can degrade slowly in acidic conditions, such as carbonated soft drinks, where approximately 50% of the content may degrade over 26 weeks. Typical maximum use levels range from 3 mg/kg in soups to 400 mg/kg in chewing gum (50).

Justification for Risk Score: A risk score of 5 is supported by the chemical's recent entry into the market and the nature of its degradation pathways. While animal studies and FDA reviews of 37 studies found no significant toxicological concerns regarding reproduction or development, the additive does break down into advantame-acid and other related substances during storage and processing. The score is further influenced by the presence of trace manufacturing impurities, such as palladium and platinum catalysts, though these are found at levels significantly lower than background dietary exposure. This score is moderated by the extremely low exposure levels required for sweetening and its lack of impact on blood sugar (50).

Carboxymethylcellulose (CMC, Cellulose Gum, E466)
Risk Score: 6
Category: Thickener/Stabilizer/Emulsifier

Health Impacts: Carboxymethylcellulose (CMC) has been shown to significantly exacerbate acute inflammatory diseases, specifically Acute Pancreatitis (AP), by inducing severe gut dysbiosis. This dysbiosis is characterized by a marked reduction in beneficial probiotics like *Akkermansia muciniphila* and *Lactobacillus*, coupled with an increase in potentially pathogenic bacteria such as *Escherichia coli* and *Bacteroides vulgatus*. Mechanistically, CMC exposure impairs the gut barrier, leading to increased leakage of Lipopolysaccharide (LPS) into the bloodstream, which activates the transcription factor C/EBPδ. This activation drives the polarization of monocytes toward a pro-inflammatory "classical" phenotype, which intensifies systemic inflammation and worsens the severity of AP (51).

Regulatory Status: Despite its widespread use, CMC was approved in the 1960s with a lack of extensive safety testing regarding its impact on the gut microbiome. It is currently authorized for use in food products at concentrations up to 2% (wt/wt) by major regulatory bodies, including the US FDA and the European Commission. While historically assumed safe because it is poorly absorbed and primarily excreted, recent studies challenge this "inert" status by demonstrating that CMC can influence human microbiota composition and promote both chronic and acute systemic inflammation (51).

Dose/Context Qualifiers: The detrimental effects of CMC are highly relevant to modern diets, as ultra-processed foods containing emulsifiers now characterize up to 60% of the Western diet. Research utilized a 1% CMC solution over a four-week period to demonstrate significant aggravation of Acute Pancreatitis, a concentration well within the levels humans may encounter daily. Furthermore, the study identifies specific biological markers for susceptibility and mitigation: a lower abundance of *Akkermansia muciniphila* in human patients is directly correlated with increased AP severity, while supplementation with either this probiotic or butyrate (a short-chain fatty acid depleted by CMC) has been shown to ameliorate the adverse effects (51).

Justification for Risk Score: A score of 6 is justified by the discovery that CMC does not merely cause "low-grade" chronic inflammation but can actively worsen life-threatening acute conditions. The evidence for this risk is robust, involving successful Fecal Microbiota Transplantation (FMT) that transferred the disease-aggravating effects from CMC-exposed mice to healthy recipients, proving the gut-mediated nature of the harm (51).

4-Methylimidazole (4-MEI)
Risk Score: 6
Category: Processing Contaminant (Caramel Color Byproduct)

Health Impacts: 4-Methylimidazole (4-MI) is a byproduct of the Maillard reaction found in coffee and soy sauce, and is also formed during the production of Class III and IV caramel colors. While the National Toxicology Program (NTP) found clear evidence of lung carcinogenicity in mice, leading to an IARC Group 2B classification, 4-MI has consistently tested negative in standard genotoxicity assays such as the Ames and micronucleus tests. Most regulatory bodies, except for California's CEPA, conclude the mechanism for tumor induction in mice is likely non-genotoxic and highly unlikely to occur at human exposure levels (52).

Regulatory Status: Regulatory views on 4-MI vary between threshold and non-threshold approaches. California's CEPA established a No Significant Risk Level (NSRL) of 29 µg/day based on a non-threshold assumption, citing a lack of comprehensive data to rule out genotoxicity in lung tissue. Conversely, the EFSA and BfR consider the effect to have a threshold, concluding that current levels in caramel colors are harmless and establishing a maximum limit of 250 mg/kg for the coloring itself (52).

Dose/Context Qualifiers: Dietary exposure to 4-MI occurs through beverages and foods like cola, coffee, and items cooked in soy sauce, though levels in soft drinks are generally low. The EFSA established a non-observed adverse effect level (NOAEL) of 80 mg/kg/day, leading to an estimated tolerable daily intake of approximately 48 mg for a 60 kg person. High consumption of certain soft drinks typically results in a maximum intake of only 0.35 mg per person, which is well below established safety limits (52).

Justification for Risk Score: The risk evaluation is centered on the discrepancy between mouse lung carcinogenicity and the lack of evidence for a genotoxic mode of action. While the IARC Group 2B classification and California’s strict NSRL highlight potential concerns, recent data and SAR software analysis support a non-genotoxic, threshold-based assessment. Consequently, most agencies conclude there is no significant health concern from the low levels of 4-MI typically consumed in soft drinks and other foods (52).

Glycidyl Fatty Acid Esters (Glycidyl Esters)
Risk Score: 8
Category: Processing Contaminant (Refined Oil Byproduct)

Health Impacts: Glycidyl fatty acid esters (GEs) are processing contaminants formed during the high-temperature deodorization of vegetable oils. Once ingested, GEs are hydrolyzed by lipases in the gastrointestinal tract, releasing free glycidol. Glycidol is a genotoxic carcinogen that has demonstrated the ability to induce tumors across various organs in animal models. Due to this sufficient evidence of carcinogenicity in experimental animals and strong mechanistic data, the International Agency for Research on Cancer (IARC) has classified glycidol as "probably carcinogenic to humans" (53).

Regulatory Status: While specific regulatory limits for various food categories are still evolving, the EFSA has officially identified GE exposure as a potential health concern. In response, the European Union established maximum levels for GEs in vegetable oils, fats, and notably, infant formula. In Japan, while no specific limits have been set, the Ministry of Agriculture, Forestry and Fisheries (MAFF) has established a "Management Plan" to monitor and reduce GEs in refined vegetable oils and processed foods (53).

Dose/Context Qualifiers: Exposure to GEs is widespread because refined vegetable oils are used in a vast array of commercially prepared foods, including fried snacks, instant noodles, and baked goods. Research indicates that fried foods often contain higher levels of GEs than non-fried foods, with potato-based snacks showing particularly high concentrations. Of particular concern is the exposure for infants through formula, as they have a higher intake relative to their body weight. Because glycidol is genotoxic, it is considered a substance for which no safe threshold can be established (53).

Justification for Risk Score: A high risk score of 8 is justified by glycidol's classification as a Group 2A carcinogen and its proven genotoxic mechanism of action. The risk is compounded by the fact that GEs are found in a wide variety of daily consumed products, from fried convenience foods to infant formula, making exposure difficult for the general population to avoid. Furthermore, because the contamination levels can vary significantly even between similar products, such as different brands of fried potatoes or instant noodles, consistent consumer safety remains a challenge (53).

Sorbic Acid/Potassium Sorbate (E200, E202)
Risk Score: 4
Category: Preservative (Antimicrobial Agent)

Health Impacts: Potassium sorbate is a widely used preservative that effectively inhibits the growth of molds, yeasts, and bacteria in various food products. While generally considered safe, excessive consumption of food additives like sorbates has been linked to potential health issues, including allergies, gastrointestinal disturbances, and hyperactivity in children. High doses of chemical preservatives may lead to toxic effects such as DNA damage or metabolic disruptions. Specifically, there are concerns regarding its genotoxic and mutagenic potential, as some studies suggest it can induce chromosomal aberrations and sister chromatid exchanges in human lymphocytes (54).

Regulatory Status: The safety and use of potassium sorbate are monitored by international health organizations to ensure consumer protection. JECFA has established an ADI for potassium sorbate of 25 mg/kg of body weight. Regulatory bodies set maximum permissible limits for its concentration in specific food categories; for example, the legal limit in fruit juices and soft drinks is often set at 200 mg/L to prevent adverse health effects (54).

Dose/Context Qualifiers: Exposure levels vary significantly based on the type of beverage and the consumer's age and weight. In studies using Monte Carlo simulations, the mean concentration of potassium sorbate found in energy drinks and fruit juices was higher than in soft drinks. Children are considered a more vulnerable group to these additives due to their lower body weight, which results in a higher chronic daily intake (CDI) compared to adults. Risk is assessed using the Hazard Quotient (HQ); an HQ of less than 1 indicates that the exposure level is within the safe range established by the ADI (54).

Justification for Risk Score: A moderate risk score is justified by the potential for some consumers, particularly high-frequency drinkers of energy and soft drinks, to approach or exceed the established safety limits. While most tested samples fall below the maximum permissible limits, the cumulative exposure from multiple food sources and the potential for long-term “cocktail effects” from consuming various additives simultaneously remain areas of concern. The vulnerability of children to higher relative doses further supports the need for careful monitoring of potassium sorbate levels in the food supply (54).

Modified Food Starch (E1404-E1452)
Risk Score: 4
Category: Thickener/Stabilizer

Health Impacts: Modified starches are primarily hydrolyzed by digestive enzymes into glucose and maltose before entering systemic circulation, while some may be fermented by gut microbiota into short-chain fatty acids. Extensive toxicological evaluations, including subchronic and carcinogenicity studies, showed no evidence of systemic toxicity, reproductive issues, or developmental harm (55).

Regulatory Status: In the United States, starch made from corn is labeled as "starch" or "cornstarch," while starches from other sources must specify their origin. Chemically altered varieties must be labeled as "food starch-modified" (57). A 2017 EFSA re-evaluation confirmed no safety concerns for the general population, concluding that an ADI is not necessary (55, 56).

Dose/Context Qualifiers: Dietary exposure to modified starches is highest in toddlers and infants with 95th percentile levels reaching 5,286 mg/kg bw per day, yet these levels stay in safe parameters. Human clinical trials show that single daily doses of up to 60,000 mg per person are well-tolerated by adults (55).

Justification for Risk Score: The low risk profile of 4 reflects that these additives are derived from standard agricultural sources, provide normal caloric energy, and are broken down into simple sugars during digestion (56). The assessment accounts for the lack of carcinogenicity or genotoxicity and recognizes that minor gastrointestinal effects at high doses are characteristic of fermentable fiber consumption rather than chemical toxicity (55).

Ethyl Maltol (E637)
Risk Score: 4
Category: Flavor Enhancer

Health Impacts: Ethyl maltol is a flavor enhancer and odor-masking agent that is almost completely absorbed from the gut and excreted in the urine as gluconamide or sulfate within two hours. Toxicological studies indicate low concern for human health, with no evidence of carcinogenicity in rats or mice and no significant treatment-related effects on fertility, gestation, or fetal development. While an initial Ames test showed uncertain results for mutagenicity in one *Salmonella* strain (TA 100), the effect was not reproducible, leading to a classification of non-mutagenic. Structure-Activity Relationship (SAR) analysis further supports a low concern for adverse effects, noting that health concerns for systemic toxicity and neurotoxicity are rated as low (58).

Regulatory Status: Effective June 2005, the EPA established an exemption from the requirement of a tolerance for ethyl maltol residues when used as an inert ingredient in pesticide formulations applied to growing crops, raw agricultural commodities, or animals. This exemption is subject to a limitation where ethyl maltol must not exceed 0.2% of the total pesticide formulation. Additionally, the FDA has classified ethyl maltol as GRAS for use as a direct food additive flavoring agent, and the JECFA established an ADI of 0–2 mg/kg body weight (58).

Dose/Context Qualifiers: Human dietary exposure is minimal due to very low use concentrations. A typical serving of ethyl maltol-containing food provides <5mg, resulting in daily intakes of 0.1-0.5 mg/kg body weight. The compound's potent flavor activity allows effective use at parts-per-million concentrations. Limited modern toxicological assessment creates some uncertainty, but adverse effects have not emerged despite decades of commercial use (58).

Justification for Risk Score: A score of 4 reflects limited comprehensive modern toxicological database, potential hepatotoxicity at high doses in animals, reliance on structural similarity to naturally occurring maltol for safety assessment, and increasing use as flavor enhancer. The low score is justified by very low dietary exposure, high-dose animal studies showing no effects within reasonable safety margins, long commercial use history without adverse signals, and JECFA conclusion of acceptable safety (58).

Sorbitol, Mannitol, Xylitol (Sugar Alcohols, E420, E421, E967)
Risk Score: 4 (General Population); Risk Amplified to 7-8 for IBS Patients
Category: Sweeteners/Humectants (Sugar Alcohols/Polyols)

Health Impacts: Sugar alcohols, or polyols, are low-calorie sweeteners that are only partially absorbed in the small intestine, with the remainder reaching the large intestine where they undergo fermentation by gut microbiota. This fermentation process can lead to gastrointestinal issues, including osmotic diarrhea, bloating, gas, and abdominal pain, particularly in individuals with pre-existing conditions like Irritable Bowel Syndrome (IBS). Beyond these effects, sugar alcohols significantly influence the gut-brain axis and metabolic health by modulating the microbiome. Specifically, they can increase the abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* while increasing the production of short-chain fatty acids (SCFAs) (59).

Regulatory Status: Sugar alcohols are globally recognized food additives; however, their regulatory consideration focuses heavily on their role as "functional" sweeteners. They are favored for their low glycemic index, making them valuable for blood glucose management in diabetic populations. Consumption is often guided by the threshold at which gastrointestinal issue distress occurs, as high intakes are known to induce laxative effects due to their osmotic properties (59).

Dose/Context Qualifiers: The physiological impact of sugar alcohols is highly dependent on the individual's gut microbiome composition and the specific type of polyol consumed. For example, erythritol is often better tolerated than sorbitol or xylitol because it is largely absorbed before reaching the colon. While acute high-dose consumption leads to predictable gastrointestinal symptoms, chronic intake at moderate levels may serve a prebiotic function, promoting the growth of health-associated microbes and enhancing metabolic homeostasis (59).

Justification for Risk Score: A risk score of 4 is justified by the dual nature of sugar alcohols: while they cause significant but non-toxic gastrointestinal distress (osmotic diarrhea and gas), they also offer therapeutic benefits, including dental protection and improved glycemic control. The score reflects that the primary "risk" is one of tolerance and digestive comfort rather than systemic toxicity. The potential for these compounds to act as prebiotics that improve the Firmicutes/Bacteroidetes ratio and increase short chain fatty acid (SCFA) production further moderates the risk, positioning them as functional ingredients with manageable side effects (59).

Xanthan Gum (E415)
Risk Score: 3
Category: Thickener/Stabilizer (Polysaccharide)

Health Impacts: Xanthan gum is a soluble fiber that is not absorbed intact and is partially fermented by gut bacteria into non-hazardous short-chain fatty acids. Chronic and carcinogenicity studies show no adverse effects even at maximum doses. While generally well tolerated, high daily intakes (~15g for a 70kg adult) can cause abdominal discomfort, increased flatulence, and bulk laxative effects (60).

Regulatory Status: Xanthan gum is authorized globally with an ADI of "not specified," indicating minimal toxicological concern. It is widely used as a thickener in processed foods, gluten-free items, and medical formulas (60).

Dose/Context Qualifiers: Refined exposure estimates for the general population reach up to 64 mg/kg body weight daily for children. Significant intake may lead to minor gastrointestinal symptoms, which the EFSA Panel considers "undesirable but not adverse" (60).

Justification for Risk Score: A score of 3 is supported by an extensive database of toxicological and clinical data spanning over 40 years. Its "not specified" ADI status is justified by its lack of systemic absorption, absence of genotoxicity, and the fact that no adverse effects were observed in long-term animal studies at maximum testing levels. While high doses can cause dose-dependent digestive discomfort, these effects are classified as undesirable rather than toxicologically adverse (60).

Cellulose/Microcrystalline Cellulose (E460)
Risk Score: 3
Category: Bulking Agent/Anti-caking Agent/Thickener

Health Impacts: Microcrystalline cellulose (E 460(i)) is an indigestible, water-insoluble linear polysaccharide that serves as a common component of plant-based fiber. It is not enzymatically digested by humans or non-herbivore mammals due to a lack of cellulases; instead, it passes through the gastrointestinal tract largely intact, with only limited microbial fermentation in the large intestine. This fermentation primarily produces short-chain fatty acids (such as acetic and succinic acid), hydrogen, carbon dioxide, and methane. While it is considered to have low toxicological concern, very high doses in rats have been associated with physiological responses like soft and pale feces. It shows no evidence of genotoxicity or carcinogenic potential (61).

Regulatory Status: Microcrystalline cellulose is authorized globally as both a food and feed additive. Major regulatory bodies, including JECFA, the Scientific Committee for Food (SCF), and the EFSA ANS Panel, have consistently allocated an ADI of "not specified," indicating that it poses no significant concern for consumer safety at intended use levels. In the European Union, it is recognized as a technological additive with functional roles as an emulsifier, stabilizer, thickener, gelling agent, and binder (61).

Dose/Context Qualifiers: The physiological role and digestibility of cellulose vary significantly by species. While humans and non-ruminants show minimal degradation, ruminants, horses, and rabbits can utilize larger amounts as an energy source through extensive fermentation in specialized chambers like the rumen or hindgut. For all species, microcrystalline cellulose is considered safe even without specific minimum or maximum content limits in diets, provided it meets food additive purity specifications (61).

Justification for Risk Score: A score of 3 is justified by its extensive safety database and its classification by JECFA, the SCF, and the EFSA ANS Panel as having an ADI of "not specified," which indicates it is of low toxicological concern. Chemically, it is a linear homopolymer identical to the natural cellulose found abundantly in plant cell walls and vegetable fiber. It is considered safe for all animal species and human consumers because it is not enzymatically digested or absorbed intact in the gastrointestinal tract; instead, it passes through the body with only limited microbial fermentation. Furthermore, toxicological evaluations confirm that microcrystalline cellulose is not genotoxic, not carcinogenic, and shows no adverse effects on reproduction or development, with NOAELs typically identified at the highest tested dosages (61).

Lecithin (E322)
Risk Score: 2
Category: Emulsifier (Phospholipid)

Health Impacts: Lecithin is a natural amalgamation of diglycerides, phospholipids, triglycerides, and glycolipids found in animal and plant tissues, including egg yolks, soybeans, peanuts, corn oil, and wheat oil. It is a vital component of all living organisms, making up more than 50% of mammalian cell membrane phospholipids and serving as a major constituent of brain and nervous tissue. Lecithin contains choline, which offers health benefits such as cognitive enhancement and liver protection from toxins. In cardiovascular health, it plays a pivotal role in reducing excess low-density lipoprotein and promoting the synthesis of high-density lipoprotein. While generally beneficial, sporadic gastrointestinal symptoms such as diarrhea and nausea have been documented (62).

Regulatory Status: Lecithin has widespread applications as a functional additive in the food industry, where it is utilized as an emulsifier, stabilizer, wetting agent, and antioxidant in products such as baked goods, confectionery, salad dressings, and margarine. Beyond food, it is used in the industrial and pharmaceutical sectors as a lubricant, dispersant, and drug delivery enhancer to improve solubility and bioavailability (62).

Dose/Context Qualifiers: Lecithin occurs naturally in significant concentrations, such as 10% of egg yolk and 2–3% of crude soybean oil. Diets enriched with lecithin have been shown to positively impact cholesterol homeostasis and lipoprotein metabolism by stimulating bile acid secretion and forming mixed micelles to facilitate cholesterol excretion. In therapeutics, it is used in lipid-based drug delivery systems and as a supplement to regulate medication release. However, its functional efficacy can be influenced by its chemical propensity to oxidize when exposed to air, potentially forming oxidative products like epoxides (62).

Justification for Risk Score: A score of 2 is supported by the fact that lecithin is a fundamental, ubiquitous biological component essential for cellular integrity and fluidity. Its primary metabolite, choline, is beneficial for cognitive and hepatic health. While high LCAT (lecithin-cholesterol acyltransferase) activity associated with lecithin metabolism is generally anti-atherogenic, some studies have debated its role, noting that increased activity can occasionally correlate with reduced LDL particle size or increased risk in specific demographics like women. Nevertheless, the risk remains low as lecithin is a natural substance found in common foods and serves as a precursor for essential biological processes.

Ascorbic Acid (Vitamin C, E300)
Risk Score: 2
Category: Antioxidant/Preservative/Nutrient

Health Impacts: Vitamin C (L-ascorbic acid) is an essential water-soluble nutrient that humans cannot synthesize endogenously. It is critical for the biosynthesis of collagen as well as L-carnitine and certain neurotransmitters. As a physiological antioxidant, it protects cells from free radical damage and regenerates other antioxidants like vitamin E. Additionally, vitamin C improves the absorption of nonheme iron from plant-based foods and plays an important role in immune function. While the body tightly controls plasma concentrations through dose-dependent active transporters, excessive intake can lead to health risks (63).

Regulatory Status: The Food and Nutrition Board (FNB) establishes Recommended Dietary Allowances (RDAs) for vitamin C based on its known physiological and antioxidant functions. For adults, the RDA ranges from 75 mg to 90 mg daily, though pregnancy and lactation increase these requirements to 80–120 mg. The FNB has also established a Tolerable Upper Intake Level (UL) for adults at 2,000 mg daily to prevent adverse health effects (63).

Dose/Context Qualifiers: At moderate intakes (30–180 mg/day), 70%–90% of vitamin C is absorbed; however, at doses above 1 g/day, absorption falls to less than 50%. Individuals who smoke require an additional 35 mg/day due to increased oxidative stress. While most people in the United States have sufficient intake, certain groups are at risk of inadequacy, including those with limited food variety, infants fed evaporated or boiled milk, and individuals with severe intestinal malabsorption or end-stage renal disease on hemodialysis. High doses of supplemental vitamin C can produce tissue and plasma concentrations that the body tightly controls, with excess unmetabolized acid being excreted in the urine (63).

Justification for Risk Score: A score of 2 is supported by vitamin C's status as an essential dietary component with a well-defined safety profile. It is naturally present in many fruits and vegetables and is commonly used in supplements with equivalent bioavailability to food sources. While acute deficiency leads to scurvy, such cases are rare in developed countries. The primary risks are associated with intakes exceeding the 2,000 mg UL, which may cause adverse effects. Furthermore, while high-dose intravenous administration is being researched for cancer treatment, oral intake is subject to strict physiological limits, and patients undergoing chemotherapy or radiation are advised to consult oncologists due to potential antioxidant interactions (63).

Tertiary Butylhydroquinone (TBHQ, E319)
Risk Score: 6
Category: Synthetic Antioxidant/Preservative

Health Impacts: TBHQ is associated with harmful effects in animals, including the induction of gastrointestinal tumors and damage to DNA rings. Long-term exposure to high doses can result

in cytotoxic, genotoxic, carcinogenic, and mutagenic effects. TBHQ can cause DNA damage, such as the development of 8-hydroxydeoxyguanosine, through the production of reactive oxygen species (ROS) like superoxide anions. It may also activate the CYP1A1 gene, which is involved in inducing carcinogenic effects. Studies indicate that TBHQ can change the function and maturation of natural killer cells. TBHQ acts against various microorganisms by disrupting cell membranes, leading to the leakage of intracellular contents and the inhibition of DNA, RNA, lipid, and protein synthesis. (64).

Regulatory Status: The JECFA has established an ADI of 0–0.7 mg/kg body weight. Maximum permitted levels vary by country, with limits of 200 mg/kg in the USA, China, Brazil, and Australia, and 120 mg/kg in Iran. Regulatory criteria require a minimum purity of 99.0% for TBHQ, with strict limits on impurities such as heavy metals (Pb, 5 ppm maximum) and hydroquinone (0.1% maximum) (64).

Dose/Context Qualifiers: TBHQ is widely used in edible oils, fats, fish, meats, cereals, dairy products (milk and cheese), mayonnaise, shortening, and snacks. Average intake levels vary globally, ranging from 50%–90% of the ADI in the USA to as high as 180% of the ADI in Australia and New Zealand. Children and infants have a higher intake of fats for their energetic requirements, which can increase their exposure; their estimated ADI is 1.3 mg/kg body weight. It is also used in cosmetics (lipsticks, hair dyes, skincare) at concentrations below 0.1% and in pharmaceutical products. More than 90% of TBHQ is absorbed after oral administration and is primarily excreted in urine as O-sulphate and O-glucuronide conjugates within 24 hours (64).

Justification for Risk Score: A high risk score of 6 is justified by evidence of gastrointestinal tumor induction and DNA damage in animal models. In some regions, human intake already reaches or exceeds 100% of the established ADI. While harmless at authorized levels, amounts exceeding these limits threaten consumer health due to cellular and molecular toxicities. Carcinogenicity is attributed to the formation of reactive species and GSH-conjugates, alongside the activation of inflammatory and apoptotic cascades (64).

Sodium Benzoate (E211, as Single Agent)
Risk Score: 6
Category: Preservative (Antimicrobial Agent)

Health Impacts: Sodium benzoate induces oxidative stress by increasing the production of reactive oxygen species (ROS) and decreasing the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT). This oxidative imbalance leads to DNA damage (mutagenicity), mitochondrial dysfunction through the reduction of mitochondrial membrane potential, and cellular apoptosis. Animal studies have shown that it can impair memory and motor coordination, cause neurotoxicity, and disrupt the hormonal balance of the HPA axis, potentially leading to increased anxiety and weight shifts (65).

Regulatory Status: Sodium benzoate is recognized as a safe food preservative (E211) when used within specific limits. The ADI is established at 5 mg/kg body weight by JECFA and EFSA. In the United States, the FDA grants it GRAS status. It is widely used in acidic environments, such as carbonated drinks, sauces, and fruit reserves, to inhibit the growth of bacteria, yeasts, and molds (65).

Dose/Context Qualifiers: Research shows that the impact of sodium benzoate is highly dose-dependent. In vitro studies on erythrocytes observed increased oxidative stress at concentrations ranging from 6.25 to 100 µg/mL. In animal models, a dose of 70 mg/kg body weight was found to be safe; however, higher doses (200, 400, and 700 mg/kg) decreased antioxidant enzyme activity, increased pro-inflammatory cytokines, and led to decreased body weight. High non-cytotoxic doses (1000 mg/mL) have been shown to decrease the functional activity of B and T lymphocytes, stop the cell cycle in the G1 phase, and inhibit lymphocyte proliferation. While average adult intake is often within safety limits, children are at higher risk, with some consuming 125%–145% of the ADI (65).

Justification for Risk Score: A score of 6 is justified by the compound's demonstrated ability to generate oxidative damage, which is a factor in neurodegenerative diseases, cancer, diabetes, and cardiovascular diseases. The score reflects evidence of mitochondrial dysfunction, DNA damage in human lymphocytes, and the disruption of the HPA axis and hormonal balance, relatively low ADI (5 mg/kg), and high population exposure (65).

Hydrolyzed Vegetable Protein (HVP)
Risk Score: 6
Category: Flavor Enhancer (Protein Hydrolysate)

Health Impacts: Hydrolyzed vegetable proteins from soy are produced through a hydrolysis process that breaks down proteins into small peptides, which reduces the molecular weight and the potential for allergic reactions. Toxicity studies on various vegetable hydrolysates show low acute oral toxicity, with no adverse effects observed in rats at doses as high as 20,000 mg/kg/day. Tests for mutagenicity, neurotoxicity, and immunotoxicity have been negative. While soy is a known allergen, the manufacturing process uses heat, pH changes, and centrifugation to remove intact proteins that cause reactions. Highly sensitive ELISA testing confirmed that no soy trypsin inhibitors were detected in the finished product, indicating a low concern for allergenicity (66).

Regulatory Status: The Environmental Protection Agency established a final rule effective May 5, 2022, that grants an exemption from the requirement of a tolerance for residues of hydrolyzed vegetable proteins from soy. This means the agency does not require a maximum permissible level for residues when the ingredient is used in accordance with specific limits. Specifically, it is approved for use as an inert ingredient acting as a pH adjusting agent, surfactant, or adhesive

in pesticide formulations. Under federal regulations, these proteins are limited to a maximum of 25% of the total pesticide formulation when applied to growing crops pre-harvest (66).

Dose/Context Qualifiers: Human exposure to these proteins can occur through dietary sources, such as food residues from pesticide use, fertilizers, or FDA-approved food additives. Non-dietary exposure may also occur through residential products like lawn and garden treatments, cosmetics, and personal care items. Because the EPA found no toxicological endpoints of concern or threshold effects in its review, it did not conduct a quantitative exposure assessment. The agency concluded that there is a reasonable certainty that no harm will result to the general population, including infants and children, from aggregate exposure to these residues (66).

Justification for Risk Score: The safety determination is supported by data showing that vegetable hydrolysates from soy have very low overall toxicity and no shared mechanism of toxicity with other chemicals. The hydrolysis process significantly reduces the risk of soy allergies, and any remaining residues on treated crops are expected to be further reduced by weather and microbial degradation before reaching consumers. Because no toxicity was observed in repeated dose studies, the EPA determined that no numerical tolerance or additional safety factors for children were necessary. The 25% limit in pesticide formulations is enforced through the federal pesticide registration process (66).

DATEM (Diacetyl Tartaric Acid Esters of Mono- and Diglycerides, E472e)
Risk Score: 5
Category: Emulsifier/Dough Conditioner

Health Impacts: DATEM E472e is a food additive used to upgrade the taste and texture of various food products (67). The U.S. FDA recognizes DATEM as a GRAS substance (67, 68). According to food manufacturers and industry assessments, eating foods containing DATEM is not harmful to human health (67). It is primarily used as an emulsifier and texturizer (68).

Regulatory Status: In the United States, DATEM is regulated under 21 CFR parts 170–186 as a GRAS substance. Its legal standing includes specific food labeling and standards regulations under 21 CFR parts 100–169 (68). It is commonly utilized by food manufacturers worldwide who consider the ingredient safe for processing (67).

Dose/Context Qualifiers: DATEM is a versatile ingredient used in a wide range of commercial food applications including yeast-fermented doughs, cakes, cookies, cereals, puffed foods, and frozen noodle products like dumplings. In bread, it is used to strengthen the gluten network and increase air-holding capacity, which is especially preferred by bakers for crusty or low-accessory breads. It is also used as an emulsifier and stabilizer in coffee creamer to prevent separation and ensure a smooth texture. Because the powder form is highly hygroscopic and prone to caking in hot or humid conditions, it is often granulated or mixed with a 20% anti-caking agent for stability during storage (67).

Justification for Risk Score: The determination of DATEM as a safe food ingredient is justified by its FDA GRAS status and its functional benefits in food processing (67, 68). It serves as an effective dispersant and anti-aging agent, particularly in baking where it enhances dough elasticity and toughness. Its ability to complex with gluten proteins and interact with starch improves the low-temperature stability of frozen foods and controls ice crystal size in pasta products. Furthermore, its foaming properties in cakes allow for stable, uniformly distributed air bubbles, resulting in a soft texture and uniform honeycomb structure (67).

Guar Gum (E412)
Risk Score: 3
Category: Thickener/Stabilizer (Galactomannan)

Health Impacts: Guar gum is practically undigested and not absorbed intact in humans; instead, it is significantly fermented by enteric bacteria in the large intestine into short-chain fatty acids. While oral intake is generally well tolerated in adults, high doses (approximately 15,000 mg per day) have been associated with abdominal discomfort. Severe clinical risks, such as esophageal obstruction or asphyxiation, are rare and primarily linked to consuming guar gum in concentrated forms like granules or pills without sufficient fluid. Despite common health claims, scientific reviews haven't established a definitive cause-and-effect relationship between guar gum intake and increased satiety, maintenance of normal blood glucose levels, or reduction of blood cholesterol (69).

Regulatory Status: The ADI for guar gum is "not specified" by both JECFA and the SCF because there is no safety concern for the general population at current exposure levels, and no numerical ADI is deemed necessary. It is widely authorized as a food additive in the EU, though it's strictly prohibited for use in "jelly mini-cups" due to the risk of choking. Current scientific data are considered insufficient to adequately assess the safety of its use in foods for special medical purposes intended for infants and young children (69).

Dose/Context Qualifiers: In the general population, the highest mean refined exposure for adults is roughly 48 mg/kg body weight per day, while high-level exposure for infants can reach up to 1,555 mg/kg body weight per day in specific medical scenarios. As a food additive, it is commonly found in dairy-based frozen products (used in 65.6% of products), sandwiches, and bread products, often appearing at levels below 0.1% in items like ice cream. Beyond standard food uses, guar gum serves as an active ingredient in medicinal products with daily dosages reaching up to 25 grams, and it is used as a satiating material in slimming products and dietary fiber supplements (69).

Justification for Risk Score: A score of 3 is justified by guar gum not being acutely toxic, genotoxic, or carcinogenic, with no adverse effects observed in subchronic rodent studies at extremely high doses up to 15,000–18,000 mg/kg body weight per day. The primary safety consideration involves dose-dependent gastrointestinal discomfort at very high intake levels (around 15,000 mg/day) and the physical risk of obstruction if consumed as a concentrated supplement with inadequate liquid. For the general population, current dietary exposure levels from food additive use remain well below the thresholds that trigger abdominal discomfort, justifying the lack of an ADI (69).

Sodium Alginate (E401)
Risk Score: 3
Category: Thickener/Stabilizer/Gelling Agent

Health Impacts: Sodium alginate is a natural anionic polysaccharide extracted from brown algae, such as giant kelp and kombu, and is valued for its high biocompatibility and degradability. It is a linear copolymer that is widely recognized for its safety in food and biomedical applications, serving as a biocompatible polymer whose immunogenicity can be influenced by its specific uronic acid composition. While it is fundamentally used for its structural properties, such as forming “egg-box” gel structures through ionic cross-linking with divalent cations like calcium, its primary role in health contexts includes serving as a functional carrier for bioactive components and drug delivery. Research indicates it can be used for environmental remediation, such as heavy metal removal and metal ion adsorption, suggesting its potential for binding substances within the gastrointestinal tract (70).

Regulatory Status: Sodium alginate is officially recognized as a safe and approved additive by major international regulatory authorities. In the United States, the FDA classifies it as a GRAS substance under 21 CFR § 184.1724, permitting its use as an emulsifier, stabilizer, and thickener. Within the European Union, it is authorized as food additive E401 under Regulation (EC) No 1333/2008. These approvals support its broad application across the food, pharmaceutical, and biomedical sectors (70).

Dose/Context Qualifiers: Sodium alginate is frequently utilized in food engineering for creating edible films, coatings, and smart packaging to extend the shelf life of fresh foods. In pharmaceutical contexts, it functions as a rate-controlling polymer in drug delivery systems, where it can be used in oral slow-release formulations to achieve controlled drug release through pH-responsive mechanisms. For example, in specific delivery systems, its swelling degree can vary significantly based on pH, such as rising to approximately 670% at pH 7.4 compared to only 110% at pH 1.2 (70).

Justification for Risk Score: The risk score of 3 is reinforced by E401’s lack of toxicity, genotoxicity, and carcinogenicity in regulatory evaluations, leading to its widespread approval as a safe food additive. Its status is supported by favorable biocompatibility and the fact that it can be modified through mild, food-compatible green chemistries, which maintain its safety for

edible applications. While it possesses strong metal ion adsorption capabilities that are beneficial for removing pollutants, these same chelation properties are managed through its established status as a GRAS substance and its long history of safe use in both food and medicine (70).

Manufactured Citric Acid (E330)
Risk Score: 2
Category: Acidulant/Antioxidant/Preservative

Health Impacts: Manufactured Citric Acid (MCA), produced via fermentation of the allergen Aspergillus niger, is linked to significant inflammatory reactions in sensitive individuals. Documented symptoms include joint pain and swelling, respiratory distress, irritable bowel symptoms, and severe enervation. These reactions are likely triggered by mold or protein by-products remaining in the final product. Unlike natural citric acid, MCA may lead to a harmful inflammatory cascade and elevated pro-inflammatory cytokines (71).

Regulatory Status: MCA is classified as GRAS by the FDA, but there is a lack of independent scientific research evaluating the safety of substantial or chronic ingestion of MCA. Despite this, it remains a ubiquitous additive in roughly 70% of the world's food and beverage supply (71).

Dose/Context Qualifiers: Citric acid is found in a wide range of products including diet sodas, energy drinks, processed dairy, and vitamins. In sensitive individuals, inflammatory symptoms typically manifest 2 to 12 hours after consumption, with severity often correlating to the amount ingested (71).

Justification for Risk Score: A score of 2 is justified by the potential for MCA to act as a systemic inflammatory trigger in susceptible individuals and its origin from Aspergillus niger, a proven human allergen. The substance has largely escaped formal safety scrutiny for nearly a century due to its GRAS designation. While most consumers do not report immediate harm, the lack of studies on chronic exposure and its possible role in the rising incidence of inflammatory and autoimmune diseases warrant a low-level cautionary score (71).

Potassium Chloride (E508)
Risk Score: 3
Category: Salt Substitute/Mineral Supplement

Health Impacts: Potassium is an essential mineral vital for nerve impulse transmission, muscle contraction, and maintaining cellular function. While it is used to manage hypertension and hypokalemia, the primary risk of administration is hyperkalemia, a life-threatening condition that can cause fatal bradycardia, ventricular fibrillation, and asystole. Vulnerable populations, particularly those with renal impairment, adrenal insufficiency, or those taking potassium-sparing diuretics and ACE inhibitors, face the highest risk. Clinical symptoms of toxicity include mental confusion, flaccid paralysis, and cardiac arrhythmias, which require immediate medical intervention and ECG monitoring (72).

Regulatory Status: Potassium salts like chloride, bicarbonate, and citrate are FDA-approved medications available in oral and intravenous forms for electrolyte replacement. Because of its potency, intravenous potassium is classified as a concentrated solution requiring dilution and should only be administered to patients with adequate hydration and urine flow. Regulatory precautions emphasize frequent serum monitoring, especially for older patients or those with impaired kidney function. While it is a routine part of maintenance fluids, its use as a medication requires strict adherence to safety protocols to prevent accidental overdose (72).

Dose/Context Qualifiers: Daily adult potassium requirements typically range from 40 to 80 mEq, with 10 mEq equaling 390 mg of elemental potassium. Dosing is highly specific: mild deficiency is treated with 10 to 20 mEq several times daily, while severe cases may require intravenous rates up to 40 mEq/hr via a central line. Pediatric doses are weight-based, usually between 1 to 5 mEq/kg/day. Because rapid intake can lead to acute toxicity, any dose exceeding 20 mEq should be divided, and high-rate infusions must be accompanied by continuous cardiac monitoring (72).

Justification for Risk Score: A risk score of 3 reflects the narrow safety margin and high mortality rate associated with potassium overdose, which can lead to rapid cardiac arrest. While potassium is an essential nutrient with significant blood pressure benefits, the risk of hyperkalemia in patients with undiagnosed or chronic renal issues is a critical concern. Toxicity management is complex, often requiring intensive care and emergency treatments like calcium gluconate or dialysis. This score balances the mineral's physiological necessity against the severe, life-threatening consequences of improper administration or impaired excretion (72).

Annatto (E160b)
Risk Score: 3
Category: Natural Color (Carotenoid)

Health Impacts: Annatto is a natural colorant derived from the seeds of the Bixa orellana plant, which is native to Central and South America. The seeds are primarily characterized by the presence of carotenoid compounds, specifically the apocarotenoids bixin and norbixin. Annatto has been used for the prevention and treatment of a wide variety of health disorders, including asthma and allergy. Modern scientific investigations have identified that these phytochemicals exhibit a range of pharmacological activities, most notably antioxidant, anti-inflammatory, and antibacterial properties. Research suggests that bixin can inhibit the increase in lipid peroxidation, supporting the plant's potential as a source of protective drugs (73).

Regulatory Status: Annatto extract and annatto are permanently listed by the FDA as color additives exempt from certification. They are approved for use in foods generally, ingested drugs generally, and external drugs and cosmetics, including those used in the area of the eye (74).

Dose/Context Qualifiers: The pulp from Bixa orellana seeds has been used for centuries across many cultures for both oral and topical applications. Typical applications include its use as a colorant and bleaching agent in various dairy and bakery food products. Aqueous leaf extracts have been studied for anti-inflammatory effects in rat models at doses ranging from 50 mg/kg to 150 mg/kg. Further systematic efforts are required to fully understand the action mechanisms and potential for adverse reactions in specific populations (73).

Justification for Risk Score: A risk score of 3 is justified because annatto is a well-established, FDA-approved natural colorant (74) with documented antioxidant and anti-inflammatory benefits. While its long history of oral and topical use supports a high safety profile, the score accounts for the ongoing need for systematic research into its specific mechanisms of action and potential adverse reactions in sensitive populations. Ultimately, the transition from traditional use to precise pharmacological application requires more robust human clinical data to fully rule out risks (73).

Beta-Carotene (E160a)
Risk Score: 2
Category: Natural Color/Nutrient (Provitamin A Carotenoid)

Health Impacts: Beta-carotene is a provitamin A carotenoid found in plant pigments that the body converts into vitamin A (retinol) in the intestine via the BCMO1 enzyme, though conversion rates may have genetic variability. Vitamin A is involved in immune function, cellular communication, growth and development, and reproduction, and supports cell growth and differentiation, playing a critical role in the normal formation and maintenance of the heart, lungs, eyes, and other organs. The body typically absorbs 10% to 30% of beta-carotene from foods, with 12 mcg of dietary beta-carotene required to provide 1 mcg of Retinol Activity Equivalent (RAE), while the body might absorb up to 75% to 100% of preformed retinol (75).

Regulatory Status: The Food and Nutrition Board has not established ULs for beta-carotene and other provitamin A carotenoids, and unlike preformed vitamin A, beta-carotene is not known to be teratogenic or lead to reproductive toxicity. However, the FNB advises against the use of beta-carotene supplements for the general population, except as a provitamin A source to prevent vitamin A deficiency. The CARET and ATBC study results suggest that large supplemental doses of beta-carotene with or without retinyl palmitate have detrimental effects in current or former smokers and workers exposed to asbestos (75).

Dose/Context Qualifiers: Most dietary provitamin A in the U.S. diet comes from leafy green vegetables, orange and yellow vegetables, tomato products, fruits, and some vegetable oils. Vitamin A is routinely added to some foods, including milk and margarine, and some ready-to-eat cereals are also fortified with vitamin A. Cooking and heat treatment can increase the bioavailability of beta-carotene from foods. About 65% to 80% of vitamin A consumed in the United States and other high-income countries comes from preformed vitamin A, whereas provitamin A is the main form consumed in low-income countries, where diets include more plant-based foods. According to NHANES III data from 1988 to 1994, approximately 26% of the vitamin A in RAEs consumed by men and 34% of that consumed by women in the United States comes from provitamin A carotenoids (75).

Justification for Risk Score: A score of 2 reflects low risk for the general population consuming beta-carotene from food sources or as a food additive at typical levels. The FNB has not established upper intake limits for beta-carotene and it is not known to be teratogenic or lead to reproductive toxicity. However, high-dose supplements (20-30 mg daily) increase lung cancer risk by 18-28% specifically in current and former smokers and workers exposed to asbestos, while among nonsmokers, beta-carotene supplements do not appear to affect the risk of cancer (75).

Stevia/Steviol Glycosides (E960)
Risk Score: 2
Category: Natural High-Intensity Sweetener

Health Impacts: Steviol glycosides from Stevia rebaudiana provide sweetness 200-300 times that of sucrose with almost no calories. Safety evaluations show no genotoxicity, carcinogenicity, or reproductive/developmental toxicity (76). Some studies suggest benefits including lowered insulin/glucose levels and improved cholesterol, though evidence is inconclusive (77). Rare side effects include digestive issues from sugar alcohol additives and potential hypersensitivity in those allergic to Asteraceae family plants.

Regulatory Status: FDA recognizes Reb-A as "generally recognized as safe"; whole-leaf stevia is not approved for processed foods (77). EU and many countries approved following safety evaluations. ADI of 4 mg/kg body weight daily established by JECFA (76). Marketed as "natural" alternatives in beverages and reduced-calorie foods.

Dose/Context Qualifiers: EFSA notes ADI could be exceeded at maximum proposed use levels (76). Commercial products often contain minimal stevia, blended with erythritol or dextrose. A 2019 study linked nonnutritive sweeteners including stevia to potential intestinal flora disruption and glucose intolerance (77). Whole-leaf stevia has different, less-studied safety profile than refined Reb-A.

Justification for Risk Score: A score of 2 reflects the limited safety data on whole-leaf stevia (not approved for commercial use), rare digestive side effects and potential hypersensitivity in Asteraceae-allergic individuals, possible disruption of intestinal flora, and concerns about kidney, reproductive, and cardiovascular effects from raw stevia herb. The low score is supported by regulatory recognition of Reb-A as safe, no evidence of genotoxicity or carcinogenicity in refined products, established ADI providing safety margins, some studies suggesting beneficial health effects, and safe use during pregnancy for Reb-A products in moderation (76, 77).

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