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Reactive Carbonyl Species in Food Systems: Comprehensive Review of Formation Pathways, Toxicological Mechanisms, and Emerging Health Risk Assessment Frameworks

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ABSTRACT: Reactive carbonyl species (RCS) represent a diverse class of electrophilic compounds ubiquitously present in environmental, dietary, and biological systems, posing significant challenges for human health risk assessment. This review systematically examines the classification, formation mechanisms, toxicological profiles, and health risk assessment frameworks for RCS, with particular emphasis on food-derived compounds. RCS are classified into three major categories: monocarbonyl compounds, polycarbonyl compounds, and α,β-unsaturated carbonyls. Each category exhibits distinct reactivity patterns and biological effects. These compounds are generated through both exogenous pathways, primarily during food processing, and endogenous metabolic processes, including lipid peroxidation, amino acid oxidation, and glycation reactions. RCS exert toxicity through multiple molecular mechanisms. These include protein carbonylation, DNA adduct formation, advanced glycation end product (AGE) generation, and disruption of cellular signaling pathways. Such molecular events contribute to the pathogenesis of diabetes, cardiovascular disease, neurodegeneration, and cancer. Human metabolism of RCS involves Phase I reactions catalyzed by aldehyde dehydrogenases and aldo-keto reductases, followed by Phase II conjugation via glutathione S-transferases. Genetic polymorphisms in these metabolic enzymes create substantial inter-individual variations in RCS susceptibility. Contemporary risk assessment approaches integrate classical food safety frameworks with mechanistic toxicology principles. Current methodologies employ benchmark dose modeling, cumulative exposure assessment, and biomarker-guided evaluation strategies. Future advancement of RCS risk assessment requires development of integrated assessment models, validation of exposure and effect biomarkers, application of physiologically-based pharmacokinetic (PBPK) modeling, and international regulatory harmonization through sustained interdisciplinary collaboration.

Keywords: reactive carbonyl species, food safety, health risk assessment, toxicological mechanisms, biomarkers, cumulative exposure

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1. Introduction

Reactive carbonyl species (RCS) constitute a class of highly reactive oxygen-containing carbonyl compounds, primarily encompassing aldehydes, ketones, and α,β-unsaturated carbonyl compounds[1–3]. These compounds are characterized by the presence of highly electrophilic carbonyl groups within their molecular structures, enabling them to undergo non-enzymatic reactions with biological macromolecules including nucleic acids, proteins, and lipids, thereby forming stable covalent adducts that subsequently alter the structure and function of these biomolecules[4]. In recent years, the escalation of environmental pollution, increased complexity of food processing technologies, and extended human lifespan have collectively contributed to growing scientific and public concern regarding RCS-associated health implications.

Food-derived RCS are predominantly generated during food processing and storage through lipid peroxidation, Maillard reactions, and caramelization processes[5]. Additionally, endogenous RCS are produced during normal metabolic processes within the human body, with their generation significantly enhanced under oxidative stress conditions[6,7]. This multi-source, multi-pathway exposure profile renders the health impact of RCS particularly complex.

Extensive research has demonstrated that excessive RCS exposure is closely associated with the onset and progression of various chronic diseases. RCS exert their toxic effects through multiple mechanisms, including the formation of advanced glycation end products (AGEs) via reactions with protein amino acid residues, DNA adduct formation leading to genetic mutations, mitochondrial dysfunction interference, and oxidative stress induction[8–10]. These molecular events subsequently trigger aberrant cellular signaling pathways, ultimately resulting in cellular and tissue dysfunction. At physiological and pathological levels, RCS have been confirmed to participate in accelerated aging processes and are implicated in the development of various metabolic diseases, including diabetes mellitus, cardiovascular diseases, neurodegenerative disorders, and multiple types of malignancies[11–14].

Despite significant advances in RCS toxicological research, health risk assessment of RCS, particularly food-derived RCS, remains in its preliminary stages and constitutes the primary focus of this review[15]. Unlike conventional food contaminants, RCS are inevitably generated during food processing, exhibit extensive diversity, and possess varied chemical properties, presenting substantial challenges for risk assessment. Furthermore, due to rapid metabolic turnover and short biological half-lives of RCS in vivo, traditional exposure assessment methodologies fail to accurately reflect actual human exposure levels. Therefore, this review aims to fill this knowledge gap by: (1) systematically summarizing the classification, source pathways, and formation mechanisms of food-derived RCS; (2) elucidating their in vivo metabolic processes and toxicological mechanisms; (3) critically evaluating current health risk assessment methodologies and their limitations; and (4) proposing emerging frameworks specifically designed for health risk assessment of food-derived RCS. While we acknowledge the importance of endogenous and environmental RCS, our primary emphasis is on food-derived RCS as a modifiable exposure route with direct implications for dietary guidelines and food safety regulations.

2. Classification, characteristics, and toxicity of RCS

Carbonyl compounds constitute a class of organic compounds containing carbonyl functional groups (C=O) that are ubiquitously distributed in environmental, food, and biological systems[16,17]. The carbonyl functional group is characterized by the double bond between oxygen and carbon atoms, which imparts a partial positive charge to the carbon atom, rendering it an electrophilic center that readily reacts with nucleophilic groups in biological macromolecules[18]. The reactivity toward nucleophiles generally follows the order depicted in Figure 1.

Based on structural characteristics and reactivity, carbonyl compounds can be classified into multiple categories. A subset of these compounds exhibits elevated chemical reactivity and is designated as RCS, defined as carbonyl compounds capable of undergoing non-enzymatic reactions with biological macromolecules[1]. For instance, RCS react non-enzymatically with biological macromolecules such as proteins, DNA, and lipids, forming stable covalent modifications that alter the structure and function of these biomolecules[19]. These modifications are closely associated with various cellular damage mechanisms, including oxidative stress, inflammatory responses, protein degradation dysfunction, and genotoxicity, thereby participating in the pathogenesis and progression of multiple chronic diseases, including diabetes and its complications, cardiovascular diseases, neurodegenerative disorders, and malignancies[20–23].

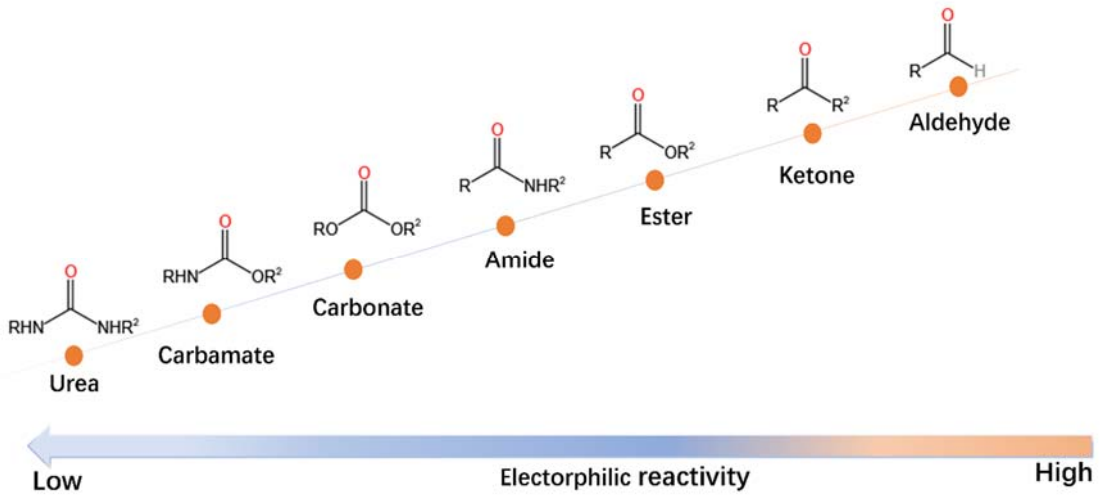


Figure 1. Reactivity order of carbonyl groups[18].

2.1 Classification and characteristics of RCS

Similar to reactive oxygen species (ROS) and reactive nitrogen species (RNS), RCS represent an important class of electrophilic stress-inducing substances capable of triggering cellular damage and tissue pathology[24]. RCS contain one or more carbonyl structures and can be categorized into monocarbonyl compounds, polycarbonyl compounds, and α,β-unsaturated carbonyl compounds (Figure 2)[1]. Currently, nearly 30 recognized RCS have been identified[25].

Monocarbonyl compounds contain a single aldehyde group (-CHO), with their reactivity derived from the electrophilic nature of the aldehyde group[26]. Formaldehyde is a highly reactive C1 compound whose unique structural symmetry and reactive carbonyl group confer greater reactivity compared to other C1

compounds, providing formaldehyde with enhanced potential for biotransformation into other chemical entities[27]. Hexanal is a monoaldehyde generated from ω-6 PUFA oxidation and exhibits relatively low reactivity compared to other RCS[28]. In various diseases, hexanal levels serve as a useful biomarker for measuring lipid peroxidation[29].

Polycarbonyl compounds are characterized by the presence of two or more carbonyl groups within their molecular structure, including malondialdehyde (MDA), glyoxal (GO), methylglyoxal (MGO), 3-deoxyglucosone (3-DG), and isolevuglandins (IsoLGs)[30]. MDA is a highly prevalent RCS produced non-enzymatically from polyunsaturated fatty acids (PUFAs) and enzymatically from prostaglandin H2 (PGH2) via thromboxane synthase, which generates MDA and thromboxane A2 (TXA2) in a 1:1 ratio[31,32]. GO and MGO are polycarbonyl compounds generated through glyoxalase-mediated oxidation of fatty acids, carbohydrates, and amino acids[33,34]. In diabetes, MGO formation is particularly prevalent, attributed to elevated glucose levels[35]. 3-DG can be synthesized through the Maillard reaction and polyol pathway and is detoxified to 3-deoxyfructose and 2-keto-3-deoxygluconate[36]. In diabetes, hyperglycemia enhances 3-DG synthesis through the Maillard reaction and polyol pathway, resulting in elevated plasma and erythrocyte levels[37]. In uremia, elevated plasma 3-DG levels may result from reduced 3-DG catabolism due to loss of 3-DG reductase activity in end-stage kidneys[38]. Reactive dicarbonyl isolevuglandins (IsoLGs) are regioisomers and stereoisomers of isoketals or 4-ketotaldehydes belonging to the prostaglandin/isoprostane family of eicosanoid-like compounds[39]. They are generated enzymatically via cyclooxygenase and non-enzymatically through lipid peroxidation[40,41]. IsoLGs react covalently with the lysyl residues of proteins, forming stable adducts and intramolecular amino, dipyrrole, and tripyrrole cross - links, which affect the occurrence of various diseases[42]. The polycarbonyl structure confers complex reactivity to these compounds, enabling crosslinking reactions with biological macromolecules that result in protein aggregation and functional impairment[43]. These compounds play crucial roles in Maillard reactions and glycation processes and are closely associated with various metabolic diseases[44].

α,β-Unsaturated carbonyl compounds are characterized by the presence of carbon-carbon double bonds at the α,β positions relative to the carbonyl carbon, including acrolein (ACR) and 4-Hydroxynonenal (4-HNE)[45,46]. These compounds possess two electrophilic centers (carbonyl carbon and β-carbon) and can react with nucleophilic groups such as sulfhydryl and amino groups in biological molecules through Michael addition reactions, forming stable covalent adducts[47,48]. Due to their unique electronic structure, α,β-unsaturated carbonyl compounds typically exhibit high biological activity. ACR is generated through in vivo oxidation of amino acids, polyamines, glycerol, and carbohydrates[49,50]. Cigarette smoke is also considered an important source of acrolein[51]. ACR undergoes non-enzymatic reactions with sulfhydryl compounds (such as glutathione or GSH, a cellular component) to form Michael adducts 100 times faster than 4-HNE[52]. The reaction between ACR and GSH is typically catalyzed by various glutathione transferases (GSTs), which appears to be a key mechanism for acrolein detoxification[53,54]. This reaction depletes GSH levels when cells are exposed to high acrolein concentrations, leading to cell death[55]. 4-HNE belongs to the

category of advanced lipid peroxidation end products[56]. As a secondary toxic messenger of free radicals, 4-HNE modifies specific amino acid residues on proteins, forming highly cytotoxic reactive 4-HNE adducts through Michael addition or Schiff base reactions[57]. Under oxidative stress conditions, 4-HNE can react with DNA through epoxidation, causing neurotoxicity and neurological diseases, ocular damage, cardiovascular injury, hepatic damage, and energy metabolism disorders[58].

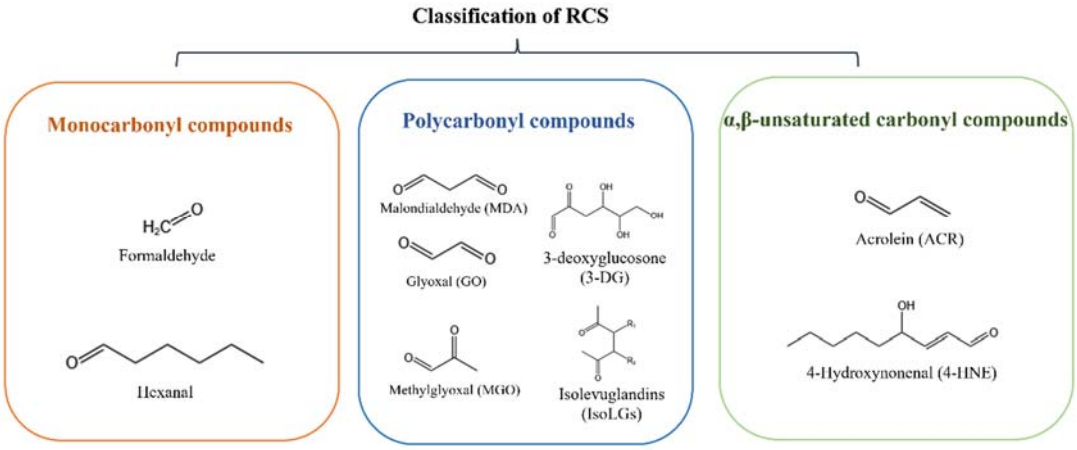


Figure 2. Classification of RCS.

2.2 Chemical reactivity and toxicity mechanisms of RCS

The chemical reactivity of RCS is primarily determined by their molecular structure and electronic characteristics. RCS exhibit four principal reaction types that underlie their biological activity. Michael addition reactions represent the characteristic reactivity of α,β-unsaturated carbonyl compounds, wherein nucleophilic groups such as sulfhydryl and amino groups on biological macromolecules preferentially attack the β-carbon position of the unsaturated system, forming covalent addition products[59]. Michael addition reactions, though involved in certain enzymatic mechanisms and cellular signaling, become toxic when RCS react indiscriminately with nucleophilic residues in critical proteins. Schiff base reactions involve addition-elimination processes between carbonyl carbon atoms and amino groups in proteins, ultimately resulting in stable imine structures[60]. While these reactions participate in normal physiological processes at physiologically controlled levels, excessive RCS-mediated Schiff base formation under pathological conditions can lead to detrimental protein modifications. Aldol condensation reactions enable certain RCS to interact with each other, generating more complex carbonyl derivatives with enhanced reactivity[61]. Additionally, specific RCS can participate in redox reactions, catalyzing the generation of reactive oxygen species (ROS) and further exacerbating cellular oxidative stress conditions[62].

Aging processes are fundamentally influenced by the cumulative effects of RCS-mediated damage throughout the lifespan. The progressive accumulation of AGEs in long-lived proteins such as collagen and elastin contributes to skin aging, joint stiffness, and reduced tissue elasticity[11,63,64]. RCS-induced mitochondrial dysfunction leads to decreased energy production and increased oxidative stress, creating a self-perpetuating cycle of cellular damage[65]. The modification of DNA repair enzymes and cellular stress

response proteins by RCS accelerates the aging process by compromising the cell's ability to maintain genomic integrity and respond to environmental stressors[66].

Furthermore, RCS-induced molecular modifications result in a variety of pathological consequences that manifest across multiple organ systems and contribute to the development of chronic diseases. At the protein level, RCS react with amino acid residues including lysine, arginine, cysteine, and histidine, leading to protein carbonylation and crosslink formation that fundamentally alters protein structure and function[67,68]. These modifications include the formation of AGEs, which accumulate progressively with age and are central to diabetic complications[69,70]. In diabetes mellitus, elevated glucose levels provide abundant substrate for RCS formation, particularly methylglyoxal and glyoxal, which react with proteins to form AGEs[71]. The accumulation of these AGEs in vascular walls, along with hemodynamic alterations, inflammatory processes, and other metabolic disturbances, contributes to the development of diabetic nephropathy[69]. Similarly, AGE accumulation in retinal capillaries leads to diabetic retinopathy, characterized by microaneurysm formation, capillary occlusion, and neovascularization[72,73].

Cardiovascular disease represents another major consequence of RCS toxicity, with multiple pathways contributing to atherosclerosis and vascular dysfunction[74]. RCS-mediated oxidation of low-density lipoproteins (LDL) and apolipoprotein B (apoB) that are readily taken up by macrophages, leading to foam cell formation and atherosclerotic plaque development[75]. HNE contributes to the atherogenicity of oxidized LDL, by forming HNE-apoB adducts that deviate the LDL metabolism to the scavenger receptor pathway of macrophagic cells, and lead to the formation of foam cells[76]. Furthermore, the relationship between AGEs-RAGE interactions and RAGE overexpression in human diabetic plaque macrophages has been shown to increase the inflammatory response, the expression of cyclooxygenase-2/prostaglandin E synthase-1, which may contribute to plaque destabilization by inducing the expression of metalloproteinases[77].

Neurodegenerative diseases demonstrate RCS toxicity due to the brain's high oxygen consumption, limited regenerative capacity, and accumulation of modified proteins over time[78].4-HNE and ACR modify specific amino acid residues in amyloid-β, promoting the formation of oligomers and fibrils that exhibit enhanced neurotoxicity[79,80]. In Parkinson's disease, RCS contribute to α-synuclein aggregation and the formation of Lewy bodies, while also damaging dopaminergic neurons through mitochondrial dysfunction and oxidative stress[81]. The modification of critical enzymes in neurotransmitter synthesis and metabolism by RCS further exacerbates neurological dysfunction, contributing to the progressive loss of cognitive and motor function characteristic of these diseases[82].

Cancer development and progression are significantly influenced by RCS through multiple carcinogenic mechanisms. At the genomic level, RCS form covalent adducts with DNA bases, particularly guanine, generating mutagenic lesions such as pyrimido[1,2-α]purin-10(3H)-one (M1G) from malondialdehyde and etheno-DNA adducts from 4-HNE[83,84]. These DNA modifications can cause base mispairing during replication, leading to point mutations, deletions, and chromosomal aberrations that drive oncogenic transformation. Furthermore, RCS-mediated activation of pro-inflammatory signaling pathways, particularly

NF-κB, creates a chronic inflammatory microenvironment that promotes tumor initiation, progression, and metastasis[85]. These multifaceted disease mechanisms establish RCS as critical mediators of aging and chronic disease development, highlighting the importance of understanding their sources, metabolism, and potential interventions for disease prevention and treatment.

Clinical and experimental evidence supports the pathological relevance of protein carbonylation across diverse disease states, with quantifiable elevations in carbonyl levels distinguishing disease from health. Plasma protein carbonyl concentrations in pediatric patients with juvenile rheumatoid arthritis (1.36 ± 0.68 nmol/mg protein) significantly exceed those in healthy controls (0.807 ± 0.16 nmol/mg protein), suggesting active involvement of carbonyl stress in inflammatory disease progression[86]. Similarly, tracheal aspirates from premature infants with extremely low birth weight (<1500 g) undergoing mechanical ventilation demonstrate elevated protein carbonyl levels (0.44 nmol/mg protein) compared to larger infants (0.29 nmol/mg protein), accompanied by increased myeloperoxidase activity indicative of neutrophil-mediated oxidative damage[87]. In acute pancreatitis, disease severity correlates with protein carbonyl burden, with severe cases exhibiting more than two-fold higher median levels (0.099 nmol/mg protein) compared to mild presentations (0.043 nmol/mg protein, $p = 0.0016$)[88]. These quantitative relationships between protein carbonyl levels and disease severity provide evidence for threshold effects wherein carbonyl accumulation beyond physiological capacity for detoxification contributes to pathological outcomes.

2.3 Relationships between RCS and other reactive species

Within biological systems, RCS, reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS) collectively constitute a complex oxidative-reductive signaling and stress network[89,90](Figure 3). Although these families of reactive species possess distinct chemical characteristics and reactivity profiles, they form a highly integrated network of signal transduction and toxicity effects within living organisms. ROS primarily encompass superoxide anion (O_2^{-}•), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and singlet oxygen ($^1O_2$), which predominantly influence biological molecules through oxidative mechanisms[91]. RNS include nitric oxide (NO), nitrite (NO_2^-), and peroxynitrite ($ONOO^-$), participating in nitration and nitrosation reactions[92]. In contrast, RCS primarily affect sulfhydryl- and amino-containing molecules through mechanisms involving Michael adduct formation and Schiff base conjugation.

Intimate biochemical transformation relationships exist between RCS and ROS, with lipid peroxidation serving as a critical bridge connecting these two species families. Under oxidative stress conditions, lipid peroxidation reactions occur predominantly in a non-enzymatic manner along the hydrocarbon chains of polyunsaturated fatty acids (PUFAs)[93]. Derivatization of auto-oxidation products with 2,4-dinitrophenylhydrazine (DNPH) followed by LC-MS/MS analysis has elucidated that both ω-3 and ω-6 fatty acids undergo peroxidation reactions. Indeed, linoleic acid and α-linolenic acid, representing ω-6 and ω-3 fatty acids respectively, have been demonstrated to generate RCS including acrolein and crotonaldehyde through peroxidation pathways[85].

Nitric oxide (NO), as a principal RNS, not only participates in signal transduction but also interacts with RCS through multiple mechanisms, establishing bidirectional regulatory networks of significant importance in inflammatory and oxidative stress-related diseases[94]. Certain RCS, particularly 4-HNE, can modulate nitric oxide synthase (NOS) activity, thereby regulating NO production[95]. Particularly noteworthy interactions exist between RCS and peroxynitrite ($ONOO^-$), formed from the reaction between NO and superoxide anion ($O_2^{-}\bullet$)[96]. Peroxynitrite can promote lipid peroxidation through multiple pathways, including direct oxidation of lipids and generation of reactive intermediates such as nitrogen dioxide ($\bullet NO_2$) and carbonate radical ($CO_3^{-}\bullet$)[97]. This enhanced lipid peroxidation consequently increases the production of RCS such as 4-HNE and MDA, creating a self-perpetuating cycle of oxidative damage.

Within the RSS family, glutathione (GSH) serves as the primary intracellular thiol compound and participates in major detoxification pathways for RCS[98]. Studies have shown that 4-HNE binds to GSH, leading to a decrease in intracellular GSH levels, which in turn impairs the cell's ability to clear other reactive substances[99]. Hydrogen sulfide (HS), representing an important RSS, enhances the activity of aldehyde dehydrogenase 2 (ALDH2), thereby facilitating cellular clearance of aldehydic RCS. This interaction represents a crucial protective mechanism, as ALDH2 catalyzes the oxidation of reactive aldehydes to their corresponding carboxylic acids, which are generally less reactive and more readily eliminated from the cell[100]. HS-mediated ALDH2 activation occurs through several mechanisms, including the sulfhydration of specific cysteine residues that enhance enzyme stability and catalytic efficiency[101]. Therefore, maintaining the balance among RCS, ROS, RNS, and RSS is crucial for cellular homeostasis. Excessive accumulation of any type of reactive substances or dysfunction of the clearance system may lead to the occurrence and development of diseases.

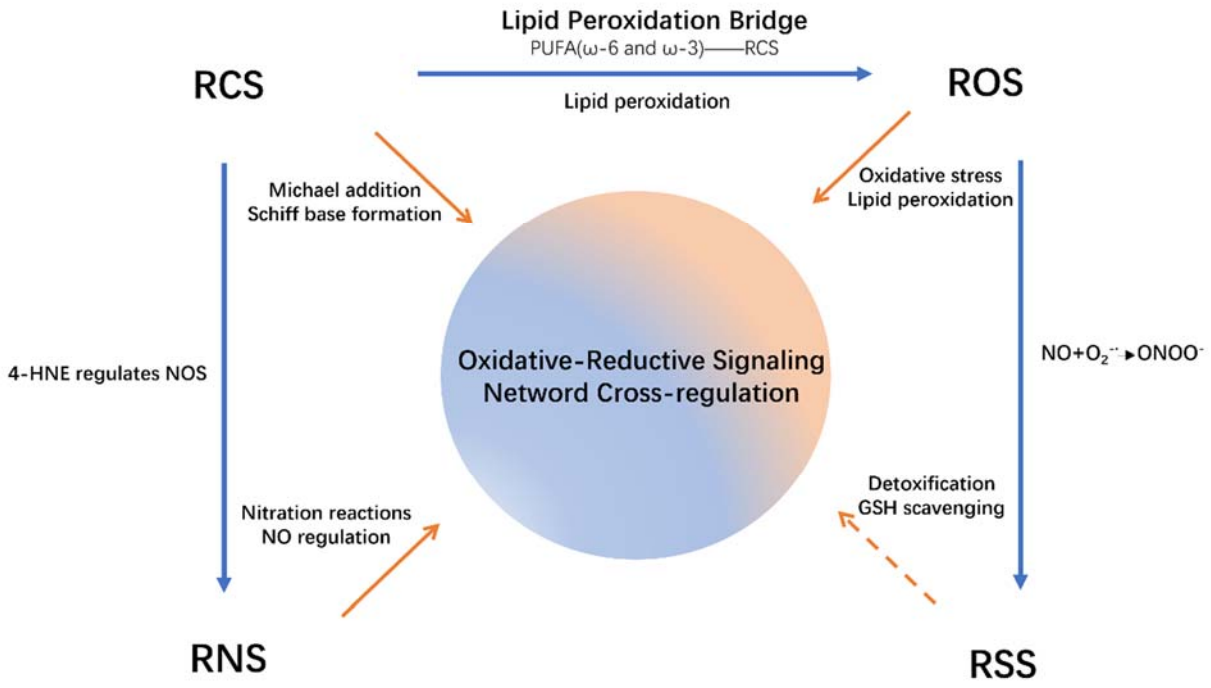


Figure 3. Reactive species interaction network (RCS-ROS-RNS-RSS).

3. The sources of RCS

RCS are ubiquitously distributed throughout our daily environment. Exogenous RCS formation, beyond environmental contamination, predominantly originates from food processing and storage procedures[5]. During thermal processing, unsaturated fatty acids undergo autoxidation under conditions of elevated temperature, oxygen availability, and metal ion catalysis, generating lipid hydroperoxides that subsequently decompose to yield aldehydic compounds[102]. The mechanistic pathway involves oxygen attack on unsaturated fatty acids in cellular membranes or lipoproteins, producing free radicals that propagate lipid peroxidation chains[103]. These processes generate lipid hydroperoxides (LOOH), which undergo metal-catalyzed decomposition to produce dialdehydes (including MDA), ketoaldehydes, α,β-unsaturated aldehydes, and alkenals[4,6]. Thermal food processing involves complex chemical transformations that enhance sensory properties, nutritional value, and shelf stability while simultaneously generating flavor compounds through Maillard reactions between reducing sugars and amino compounds. The Maillard reaction is a series of oxidation, cyclization, dehydration and polymerization reactions between carbonyl compounds and amino compounds, and it is an important reaction for the formation of food flavor substances[104]. However, inadequate process control can result in excessive formation of potentially harmful derivatives, including AGEs[105]. The specific combination of reducing sugars and amino acids significantly influences RCS generation patterns. Systematic studies examining glucose, fructose, maltose, and lactose reactions with lysine, threonine, cysteine, and serine have demonstrated that fructose-threonine systems produce the highest concentrations of unsaturated carbonyls, while lactose-cysteine systems yield minimal levels[106]. In glucose-leucine model systems, 1-deoxyglucosone (1-DG) and 3-deoxyglucosone (3-DG) formation occurs through enolate intermediates, with 1-DG undergoing cleavage to acetaldehyde and subsequent glyoxal oxidation, while 3-DG can generate 5-hydroxymethylfurfural (HMF)[107]. Processing methods significantly impact RCS formation, with frying, baking, and grilling producing substantially higher Maillard product yields compared to steaming, reflecting the influence of temperature and water activity on reaction kinetics[108–111]. Low-temperature processing also contributes to RCS formation through freeze-thaw cycling, which enhances lipid oxidation and RCS generation in meat products[112]. The interaction between Maillard reactions and lipid oxidation at reduced temperatures demonstrates the complex nature of RCS formation across diverse processing conditions.

Fermentation processes present additional complexity in food-related RCS formation, with outcomes varying significantly based on microbial species, substrate composition, and environmental conditions. Alcoholic fermentation by Saccharomyces cerevisiae and malolactic fermentation by lactic acid bacteria in wine production generate various RCS including glyoxal, methylglyoxal, and volatile sulfur compounds[113]. The enzymatic activity of malolactic enzyme, containing dual NAD-binding domains, catalyzes the formation of acetoin, diacetyl, and acetaldehyde during malolactic fermentation[114]. In other fermented products such as pickled vegetables, soy sauce, and fermented pastes, microbial aminotransferases convert amino acids to α-keto acids, which undergo decarboxylation to yield corresponding RCS that contribute to characteristic

flavors[115]. The dual nature of fermentation effects on RCS content reflects competing formation and degradation pathways. Fermentation can reduce RCS levels through substrate degradation, antioxidant production, or conjugation reactions that decrease toxicity[116,117]. Conversely, enhanced substrate breakdown, aldehyde generation, or promoted Maillard reactions can increase RCS concentrations[118]. The net effect depends on microbial specificity, enzymatic activity, and process conditions, highlighting the importance of controlled fermentation parameters in managing RCS content in fermented foods.

Endogenous formation of RCS represents a complex network of enzymatic and non-enzymatic biochemical processes occurring within cellular environments. These pathways generate diverse intracellular reactive species through three principal mechanisms: lipid peroxidation cascades, amino acid oxidative degradation, and glycation reactions. Understanding these endogenous sources and their relative contributions is crucial for comprehensive assessment of RCS health risks, as different formation pathways yield compounds with distinct chemical properties and toxicological profiles (Figure 4).

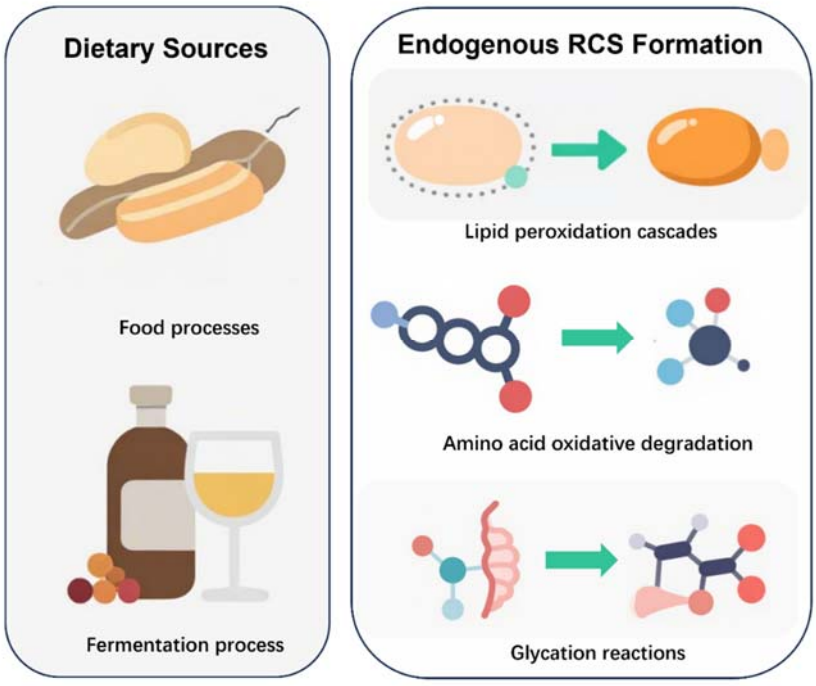


Figure 4. The multisource nature of RCS exposure.

3.1 Lipid Peroxidation Pathways

Free radical-mediated degradation of polyunsaturated fatty acids (PUFAs) within triglycerides, phospholipids, and cholesteryl esters constitutes a fundamental mechanism of endogenous RCS generation. This oxidative process yields a spectrum of aldehydic compounds including hexanal, acrolein, crotonaldehyde, 4-HNE, glyoxal, 4-oxo-trans-2-nonenal (ONE), trans-2-nonenal, and MDA(Figure 5)[119]. Quantitative analysis reveals that MDA, hexanal, and HNE contribute approximately 70%, 15%, and 5% respectively to the total aldehyde yield from lipid peroxidation processes[52]. Pathological conditions significantly amplify RCS production through enhanced lipid peroxidation, establishing these compounds as valuable biomarkers for oxidative damage and disease progression.

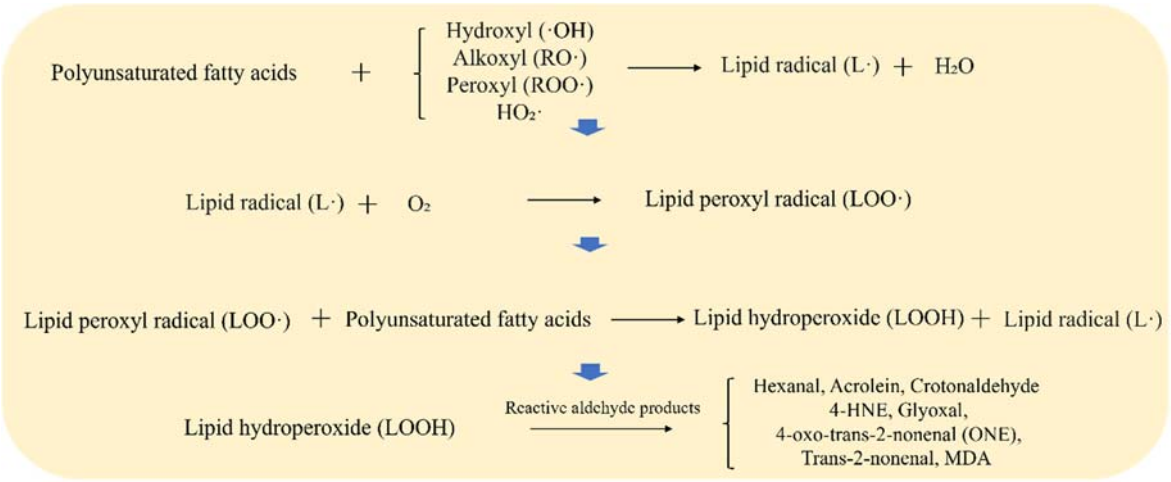


Figure 5. Lipid peroxidation cascade generating RCS. Free radical-initiated oxidation of polyunsaturated fatty acids proceeds through initiation (hydrogen abstraction by ·OH, RO·, ROO·, HO2·), propagation (formation of lipid peroxyl radicals, LOO·), and decomposition of lipid hydroperoxides (LOOH) to yield aldehydic products.

3.2 Amino Acid Oxidative Metabolism

Protein carbonylation through amino acid oxidative degradation represents an irreversible modification typically resulting from pro-oxidative environments and oxidative stress conditions (Figure 6). The "Stadtman pathway" describes the direct oxidative introduction of carbonyl derivatives, including aldehydes and ketones, into proteins through specific amino acid side chain modifications[120]. ROS preferentially target basic amino acids including proline, arginine, lysine, and threonine, initiating hydrogen atom abstraction from adjacent carbon centers[25]. This oxidative attack generates unstable imine intermediates that undergo spontaneous hydrolysis to form corresponding protein carbonyls. Mechanistic studies demonstrate that proline oxidation yields 2-pyrrolidinone, while combined arginine and proline modifications produce glutamic semialdehyde. Lysine generates α-aminoadipic semialdehyde, and threonine oxidation results in 2-amino-3-ketobutyric acid formation[121]. Specialized enzymatic pathways contribute significantly to endogenous carbonyl generation through amino acid catabolism.

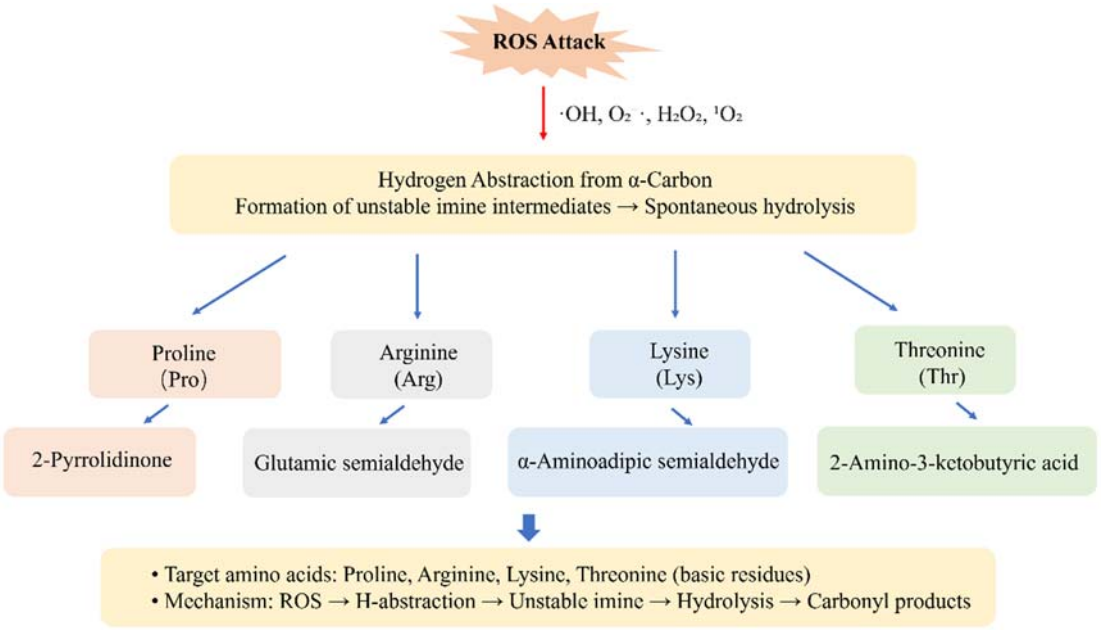


Figure 6. Stadtman pathway of protein carbonylation through amino acid oxidative metabolism.

3.3 Glycation Processes

Reducing sugars undergo spontaneous reactions with amino groups of amino acids such as arginine and lysine through Maillard reaction pathways, initially forming Schiff bases that mediate subsequent rearrangements yielding AGEs[122,123]. Enhanced glycolytic flux elevates methylglyoxal and glyoxal concentrations, facilitating protein-amino acid interactions that amplify AGE formation[124]. This cascading process increases α-oxoaldehyde levels (sugar oxidation products), potentially exacerbating chronic disease pathology. Furthermore, Enzymatic carbohydrate metabolism pathways generate specific RCS through distinct mechanisms. Enzymatic carbohydrate metabolism also contributes to RCS production via distinct pathways: the polyol pathway generates 3-deoxyglucosone during glucose-to-fructose conversion, while the glycolytic pathway is the primary source of methylglyoxal[125,126]. Non-enzymatic glycation involves reducing carbohydrates including fructose and glucose, a process potentially attributed to excessive dietary carbohydrate intake or adverse metabolic conditions[127,128].

The multisource nature of RCS exposure, encompassing dietary intake and endogenous metabolic generation, collectively determines human RCS exposure profiles. Different formation pathways produce compounds with varying chemical characteristics and toxicological potential, necessitating differentiated assessment approaches. Furthermore, cumulative effects from multiple exposure sources represent critical factors requiring consideration in comprehensive health risk evaluation frameworks.

4. Metabolic Processes of RCS

Having established the multisource nature of RCS exposure from both exogenous and endogenous pathways, understanding how the human body processes these reactive compounds is crucial for assessing their health risks. Following human exposure, RCS undergo sophisticated metabolic processes encompassing absorption, distribution, biotransformation, and elimination pathways. The efficiency and characteristics of these processes fundamentally determine toxicological expression and potential health risks associated with RCS exposure. Understanding these metabolic pathways provides critical insights into individual susceptibility variations and establishes foundations for biomarker-based exposure assessment strategies.

4.1 Absorption and Distribution Characteristics

Multiple exposure routes facilitate RCS entry into systemic circulation, each exhibiting distinct absorption kinetics and efficiency profiles. The gastrointestinal tract serves as the predominant absorption site for dietary-derived RCS, with low molecular weight aldehydes including formaldehyde, acetaldehyde, and acrolein demonstrating enhanced absorption efficiency[129]. Studies reveal that these small molecular weight compounds traverse intestinal epithelial cell membranes through simple diffusion processes, while higher molecular weight species such as 4-HNE require carrier-mediated transport mechanisms for systemic entry[130]. Respiratory absorption represents the primary pathway for environmental and occupational RCS exposure scenarios. Gaseous aldehydic substances undergo extensive absorption within upper respiratory tract mucosa, though smaller fractions penetrate to alveolar regions for systemic uptake[131]. Notably, airway

mucosa contains abundant aldehyde metabolizing enzyme systems that provide concurrent metabolic processing during absorption, constituting the initial defensive barrier against RCS toxicity[132]. Dermal absorption contributes to RCS uptake, particularly relevant for occupational populations. Lipophilic RCS can penetrate the stratum corneum to reach epidermal and dermal layers, though absorption rates remain substantially lower compared to gastrointestinal and respiratory routes[133]. Following systemic entry, RCS distribution patterns correlate closely with their physicochemical properties and inherent reactivity toward nucleophilic cellular components[134]. α,β-unsaturated RCS typically exhibit reactivity levels approximately one order of magnitude greater than their saturated counterparts[135,136]. Consequently, biological damage predominantly associates with α,β-unsaturated aldehydes, dialdehydes, and ketoaldehydes.

4.2 Biotransformation and Elimination Pathways

Human detoxification of RCS involves sophisticated enzymatic systems operating through sequential Phase I and Phase II metabolic reactions. This multi-phase approach ensures efficient neutralization and elimination of potentially toxic carbonyl species while maintaining cellular homeostasis.

Oxidative and reductive transformations constitute the primary Phase I reactions for RCS detoxification[137]. Aldehydic substrates undergo oxidation to corresponding carboxylic acids or reduction to alcoholic derivatives through specialized enzyme systems. The aldehyde dehydrogenase (ALDH) superfamily represents the cornerstone of Phase I carbonyl metabolism, comprising 19 functionally characterized genes that catalyze diverse aldehydic substrate oxidations[138]. ALDH superfamily member mutations or aberrant expression patterns frequently result in pathological conditions, emphasizing their critical functional importance[139]. ALDH2, highly expressed in hepatic tissue, exhibits particular pathophysiological significance due to polymorphic variations and altered expression levels[140]. The ALDH2*2 variant (rs671), present in approximately 40% of East Asian populations, causes near-complete enzymatic activity loss (approximately 90% reduction), rendering carriers susceptible to aldehyde-related toxicity[138]. This functional deficiency manifests across multiple organ systems: acute alcohol intake (0.4 ml/kg) in ALDH2-deficient individuals induces autonomic nervous system dysregulation with elevated catecholamine secretion when blood acetaldehyde reaches 10-fold higher levels than in ALDH2-normal subjects; chronic effects include 1.20-fold elevated type 2 diabetes risk in hypertensive patients (adjusted OR: 1.203, 95% CI: 1.013-1.428) and toxic aldehyde accumulation in neuronal tissues[141–143]. Cancer susceptibility demonstrates striking gene-environment interactions: for esophageal cancer, ALDH2*1/*2 carriers show dose-dependent risk escalation from never drinkers (OR = 1.21) to light drinkers (OR = 3.79) to heavy drinkers (OR = 6.50, 95% CI: 5.34–7.92), while ALDH2*2/*2 homozygotes who consume alcohol face 3.87-fold elevated risk despite protective effects when abstaining[144].

Complementary reductive pathways involve aldo-keto reductase (AKR) superfamily members, NAD(P)H-dependent oxidoreductases predominantly localized within cytoplasmic compartments[145]. These enzymes catalyze RCS reduction to corresponding alcoholic compounds, converting aldehydes to primary alcohols and ketones to secondary alcohols, establishing alternative detoxification routes[146,147].

The study found that in rats with diabetic retinopathy (DR), the activity of AKR in the retina was abnormal, which may be one of the important mechanisms for the increase in carbonyl stress[148].

Phase II metabolism enhances the water solubility of RCS through conjugation reactions mediated by glutathione S-transferase (GST) to promote their excretion[149]. GSTs primarily catalyze coupling reactions between reduced glutathione (GSH) and electrophilic RCS, forming GSH conjugates that undergo subsequent metabolic processing[150]. Although RCS-GSH conjugates retain inherent toxicity, GST-catalyzed conjugate formation constitutes an essential detoxification step. Specific conjugates undergo AKR1B1-mediated reduction to GS-DHN derivatives for cellular elimination, completing the detoxification cascade[151]. Water-soluble carboxylic acid metabolites and GSH conjugates enter renal elimination pathways for direct urinary excretion. Urinary metabolite analysis reveals diverse RCS-GSH adducts and their metabolic derivatives, including 3-hydroxypropyl-mercapturic acid (3-HPMA), representing acrolein metabolic products that serve as exposure biomarkers[152]. Respiratory elimination constitutes an alternative excretion route, particularly significant for low molecular weight, highly volatile RCS. Clinical studies demonstrate significant differences in exhaled acetaldehyde and acetone concentrations between preterm and full-term infants, reflecting varying carbonyl stress states[153]. Incompletely metabolized formaldehyde, acetaldehyde, and acrolein undergo partial elimination through exhaled breath.

The sophisticated metabolic machinery for RCS processing involves multiple enzymatic systems and elimination pathways, constituting essential defensive mechanisms against RCS toxicity. Comprehensive understanding of these metabolic foundations and regulatory mechanisms provides crucial insights for assessing individual susceptibility variations and health risk evaluation. Furthermore, RCS metabolites serve as valuable biomarkers for exposure assessment, facilitating development of more precise health risk evaluation models and personalized risk management strategies.

5. Health Risk Assessment Methodologies for RCS

The health risk assessment of RCS represents a challenge requiring harmonization of classical food safety frameworks with contemporary health-focused methodologies. Unlike conventional food contaminants with discrete exposure sources and well-defined toxicological endpoints, RCS present unique assessment complexities arising from their dual endogenous-exogenous origins, diverse formation pathways, and involvement in chronic disease processes.

5.1 Evolution of Food Chemical Risk Assessment Paradigms

Contemporary risk assessment methodologies have undergone substantial evolution from threshold-based approaches toward comprehensive frameworks addressing cumulative exposure scenarios. The classical paradigm, established by the Codex Alimentarius Commission and National Research Council, employs a systematic four-step process encompassing hazard identification, hazard characterization, exposure assessment, and risk characterization. Traditional approaches prioritized acute toxicity thresholds such as Acceptable Daily Intake (ADI) values, derived from no-observed-adverse-effect levels (NOAELs) in animal studies with applied safety factors[154]. However, modern iterations increasingly adopt probabilistic

modeling approaches, including Monte Carlo simulations, to address multi-chemical exposures and data uncertainties. Next-generation risk assessment (NGRA) strategies integrate high-throughput screening methodologies and Threshold of Toxicological Concern (TTC) principles for chemical prioritization, leveraging exposure-driven tools such as the Flavours, Additives, and food Contact materials Exposure Tool (FACET) for efficient risk triage[155]. For RCS evaluation, this methodological progression proves particularly critical given their complex formation mechanisms and metabolic interactions requiring dynamic models that account for biochemical pathways and dietary matrix effects[156,157]. The benchmark dose (BMD) methodology involves mathematical fitting of dose-response datasets to estimate doses associated with predefined effect levels, typically a 10% increase in toxic outcomes, along with lower confidence limits (BMDL) serving as reference points for risk assessment[158]. This approach provides superior statistical rigor compared to traditional NOAEL derivations, particularly for low-dose extrapolation scenarios relevant to chronic RCS exposure.

Quantitative risk evaluation of food-borne RCS requires sophisticated integration of exposure data with mechanistic toxicological information. Recent developments in exposure assessment methodologies include comprehensive databases of AGEs in common foods, developed through LC-MS spectrometry analyses[24]. These databases enable population-level exposure estimation for specific RCS compounds, facilitating targeted risk assessment calculations. Acrylamide exemplifies successful implementation of modern RCS risk assessment principles. Extensive European monitoring programs have enabled precise estimation of average dietary acrylamide intakes, typically ranging from tens to hundreds of micrograms per day across different population groups[159,160]. These intake estimates, combined with BMD modeling of animal carcinogenicity data, support margin of exposure (MOE) calculations for risk characterization[161,162]. The European Food Safety Authority's 2015 assessment concluded that acrylamide intake poses potential health concerns, prompting implementation of benchmark levels for specific food categories and ongoing development of regulatory maximum limits[163]. Risk management frameworks for acrylamide incorporate exposure data, toxicological modeling, and achievable mitigation strategies, requiring food businesses to maintain levels below established benchmarks and implement corrective measures when exceeded. This comprehensive approach demonstrates successful integration of scientific risk assessment with practical regulatory implementation.

However, acrylamide represents a notable exception in an otherwise incomplete regulatory landscape for food-derived RCS. In contrast, other dietary RCS currently lack specific regulatory limits or benchmark guidelines, leaving potent toxicants including 4-HNE, methylglyoxal, and crotonaldehyde unregulated despite their ubiquitous presence in thermally processed foods. While sharing similar formation pathways and toxicological profiles with acrylamide, regulatory bodies have not established exposure limits for these compounds due to insufficient consensus regarding their contributions to human disease burden[164–166].

This regulatory gap reflects several fundamental challenges that complicate RCS risk assessment beyond the acrylamide model. Current single-compound evaluation paradigms inadequately address mixture

reality—dietary exposure involves simultaneous intake of multiple structurally related carbonyls potentially sharing common mechanisms of toxicity, yet cumulative risk assessment frameworks have not been implemented. The MOE approach successfully applied to acrylamide demonstrates methodological feasibility but requires substantial adaptation for compounds with significant endogenous formation: methylglyoxal production from glycolysis exceeds typical dietary intake by orders of magnitude, yet risk frameworks have not resolved how to integrate exogenous and endogenous exposures, particularly for metabolically compromised individuals such as diabetic patients with elevated basal carbonyl production. Furthermore, standard uncertainty factors may inadequately protect genetically susceptible subpopulations such as ALDH2*2 carriers who exhibit substantially impaired aldehyde detoxification capacity, yet current regulatory limits do not account for such polymorphisms. These challenges highlight the need for expanded risk assessment efforts addressing the broader spectrum of food-borne RCS through integrated approaches that consider mixture effects, endogenous-exogenous exposure interactions, and inter-individual metabolic variability.

5.2 Exposure Assessment and Cumulative Risk Modeling

Contemporary RCS risk assessment increasingly relies on sophisticated exposure characterization methods that integrate biomarker-based monitoring with cumulative assessment approaches. Validated biomarkers provide integrated measures of multi-route RCS exposure, with urinary metabolites such as 3-HPMA from acrolein metabolism serving as specific indicators of individual exposure levels[152]. Advanced analytical techniques enable simultaneous quantification of multiple RCS metabolites, providing comprehensive exposure profiles accounting for both dietary and endogenous sources. Physiologically-based pharmacokinetic (PBPK) modeling enhances biomarker interpretation by predicting internal dose metrics from external exposure estimates, incorporating metabolic pathway information to translate between measured biomarker concentrations and biologically effective doses at target tissues[167–169]. Recognition of concurrent dietary RCS exposures has prompted development of cumulative risk assessment methodologies addressing combined effects of multiple compounds. Correlation analyses demonstrate significant associations between intake levels of different RCS compounds, with correlation coefficients ranging from 0.7-0.8 between acrylamide and polycarbonyl compounds in typical diets[160,170,171]. Cumulative assessment methodologies employ relative potency factor approaches, grouping compounds based on common modes of action and expressing them as toxic equivalents relative to index compounds[172,173]. Monte Carlo simulation techniques enable probabilistic assessment of cumulative exposures, incorporating variability in consumption patterns, food concentration levels, and individual susceptibility factors to provide distributions of exposure estimates supporting nuanced risk characterization decisions[154].

5.3 Population-Specific Risk Assessment

Modern RCS risk assessment integrates mechanistic understanding of toxicity pathways with population-specific considerations to develop more accurate and protective risk models. Risk assessment

methodologies increasingly recognize differential susceptibility among population subgroups requiring tailored evaluation approaches. Diabetic individuals exhibit elevated endogenous carbonyl stress, potentially increasing vulnerability to dietary RCS exposure through compromised detoxification capacity and enhanced oxidative stress states[7,174,175]. Populations with genetic polymorphisms affecting RCS metabolism, such as the ALDH2-rs671 variant in East Asian populations, demonstrate altered toxicokinetic profiles necessitating adjusted risk characterization frameworks[176]. Pediatric populations present unique assessment challenges due to developmental stage-specific consumption patterns, enhanced metabolic rates, and critical susceptibility windows during organ development[177]. Age-specific exposure factors, toxicokinetic parameters, and safety factors require systematic incorporation into risk models to ensure adequate protection of vulnerable life stages. Pregnancy and lactation represent additional sensitive periods requiring specialized consideration due to potential transgenerational effects and altered maternal metabolism patterns[178,179].

The evolution of risk assessment methodologies from threshold-based approaches toward integrative frameworks reflects growing recognition of cumulative exposure scenarios and mechanistic understanding of RCS toxicity. The successful implementation of acrylamide risk management through monitoring programs, benchmark levels, and mitigation strategies demonstrates the feasibility of science-based regulatory approaches for food-derived RCS[152]. However, the majority of food-related RCS compounds remain without specific regulatory oversight, highlighting the need for expanded risk assessment efforts. Future advancement in RCS risk assessment requires continued development in several critical areas. Enhanced exposure assessment tools, including improved prediction algorithms for food processing-related RCS formation and expanded biomarker validation studies, will support more accurate exposure characterization.

6. Conclusion

RCS represent critical mediators of human health risks through complex multi-source exposure scenarios involving environmental pollution, food processing, and endogenous metabolism. The diverse structural classes of RCS—monocarbonyl, polycarbonyl, and α,β-unsaturated compounds—exhibit distinct formation pathways and toxicological mechanisms, including protein carbonylation, DNA adduct formation, and advanced glycation end product generation, contributing to chronic diseases such as diabetes, cardiovascular disease, neurodegeneration, and cancer.

Several limitations constrain current epidemiological evidence for RCS health effects. First, most studies measure single RCS compounds or AGEs, failing to account for cumulative exposure to multiple related compounds. Second, endogenous RCS production, which may exceed dietary intake in certain pathological states, is rarely quantified in epidemiological studies. Third, the long latency period between exposure and chronic disease outcomes necessitates decades-long prospective studies.

Human metabolic capacity for RCS detoxification through aldehyde dehydrogenases and glutathione conjugation systems varies substantially due to genetic polymorphisms, necessitating population-specific risk assessment approaches. Contemporary evaluation frameworks have evolved from threshold-based methods to

integrated approaches employing benchmark dose modeling, cumulative exposure assessment, and mechanistic toxicology, exemplified by successful acrylamide risk management strategies. Future advancement requires continued development of validated biomarkers, physiologically-based pharmacokinetic models, and harmonized international regulatory frameworks through sustained interdisciplinary collaboration combining analytical chemistry, toxicology, epidemiology, and food science. The inherent complexity of RCS exposure and toxicity underscores the critical need for evidence-based strategies that effectively mitigate health risks while preserving essential food processing benefits, ultimately protecting public health in an increasingly complex chemical environment.

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Declaration of competing interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this study.

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