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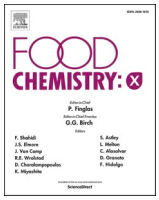

Occurrence, formation mechanism, detection methods, and removal approaches for chloropropanols and their esters in food: An updated systematic review

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ABSTRACT

Chloropropanols, one of the major contaminants in food, and the corresponding esters or glycidyl esters (GEs) are of great concern in terms of product safety due to their potential carcinogenicity. During heat processing, glycerol, allyl alcohol, chloropropanol esters, sucralose, and carbohydrate in mixed foodstuffs are probable precursors of chloropropanol. The standard analytical techniques for chloropropanols or their esters are GC–MS or LC-MS following sample derivatization pretreatment. By comparing modern data against that five-year-old before, it appears that the levels of chloropropanols and their esters/GEs in food products have somewhat decreased. 3-MCPD esters or GEs may yet exceed the permitted intake set, however, especially in newborn formula which requires particularly stringent regulatory measures. Citespace (6.1. R2) software was employed in this study to examine the research focii of chloropropanols and their corresponding esters/GEs in the literature.

1. Introduction

As food toxicants, chloropropanols in foodstuffs are of great concern for consumers owing to their intrinsic carcinogenic toxicity and ubiquity (European Commission, 2001; European Commission, 2020). There are four types of chloropropanols with one or two chlorine atoms in position 1 or 2 in glycerol, namely, with prefix of mono- or di-; they include 3-monochloropropane-1,2-diol (3-MCPD), 2-monochloropropane-1,3-diol (2-MCPD), 1, 3-dichloropropane-2-diol (1, 3-DCP), and 2, 3-dichloropropane-1-diol (2, 3-DCP), as shown in Fig. S1 (Jedrkiewicz et al., 2016).

In 1978, Velisek et al. firstly discovered 3-MCPD in acid-hydrolyzed vegetable proteins (HVPs) used to make soy sauce (Velisek et al., 1978). Its corresponding esters were found soon after and have since attracted a lot of research interest (Velisek et al., 1980). Later, free chloropropanols and their fatty esters were found in heated food, infant formula, margarine and related food matrices, fried cereal food, and vegetable oil. Data for the aforementioned four types of chloropropanols in toxicological investigations are relatively varied due to inherent variations in their structural characteristics (Olsen, 1993; Andres et al., 2013; Lynch et al., 1998). 3-MCPD is of particular interest to scientific researchers currently due to its prevalence and relative abundance in food products. Most of the harmful side effects of chloropropanol esters that are produced by the esterification of chloropropanol with fatty acids are uncertain, except for those of 3-MCPD ester and 1, 3-DCP ester.

As shown in Table S1, expert committees have issued toxicological data for chloropropanols. It is accepted that the in vitro genotoxic activity is not expressed in vivo (Fellows, 2000; Marshall, 2000; JECFA, 2001; EC, 2001; COM, 2000; COC, 2000; S. C. O,2001). Tolerated daily intake (TDI) data has fluctuated over time with regard to 3-MCPD. First, in 2001, the Scientific Committee for Food (SCF, 2001) set a TDI value of 2 μg/kg·bw/day. In 2016, the European Food Safety Authority (EFSA, 2016) set a TDI value of 0.8 μg/kg·bw/day. In 2016, the World Health Organization (WHO) and Food and Agriculture Organization (FAO) of the United Nations set a maximum TDI value of 4 μg/kg·bw/day for 3-MCPD and its corresponding esters singly or in combination

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(expressed as 3-MCPD equivalents). As recently as 2018, the EFSA updated the TDI value to 2 μg/kg·bw/day. Table 1 lists the limit ranges imposed by several authorities. Only the TDI of chloropropanol has been established by authorities; the limit requirements for chloropropanol esters or GEs in food products have not yet been established.

GEs, conversely, which were first reported in 2009, have raised even more concern as per their potential to release the genotoxic carcinogen glycidol in animal studies (Weiβhaar and Perz, 2009). The present European Commission (EC) is anticipated to update the established limits for the permissible amount of 3-MCPD in soy sauce and hydrolyzed vegetable proteins in addition to the maximum levels of GEs in vegetable oil and infant formula. Chloropropanols are mainly found in ready-to-eat foods, where several reports have identified them as hazardous.

To safeguard public health and provide the groundwork for future research, it is necessary to fully understand the relevant properties of chloropropanols in food. This requires detailed, up-to-date, thorough data for chloropropanols, their related fatty esters, and GEs in food products. A summary of existing data is given in Fig. 1. The summary was established based on the literature from 2000 to 2022 in the Web of Science, Springer, and Wiley databases using the search terms "chloropropanol," "MCPD," "DCP," and "ester". Our goal is to systematically and comprehensively summarize (i) the potential mechanisms of formation, i.e., why these pollutants are present in food; (ii) the analytical techniques used to gather this data; (iii) the presence of these toxicants in foodstuffs and how they affect healthy, safe diets; (iv) the methods of removing chloropropanols to lessen their potential harm. Citespace (6.1. R2) software was employed to process the collected data to better understand the research to date on chloropropanols and their corresponding esters or GEs.

2. Previous research

Our Citespace analysis findings for chloropropanol research projects are shown in Fig. S2. In recent decades, the focus of research on chloropropanol in foods has changed. As shown in Fig. S2, the research on chloropropanols was initially focused on 3-MCPD, 2-MCPD, 1, 2-MCPD ester, 1, 3-DCP, 1, 2-DCP, and their exposure, nephrotoxicity, and pathogenic mechanism (Caco-2 model). 3-MCPD ester was identified as a potential hazard contaminant in food by a worldwide symposium convened by International Life Sciences Society (ILSI Europe), in collaboration with the EC. Since then, research focii have gradually shifted to formation mechanism, analysis methods, occurrence, and elimination methods.

Pathogenic mechanism

According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the kidney is the primary organ affected by 3-MCPD toxicity. Chronic oral exposure causes nephropathy, tubular hyperplasia, and adenomas (Food and Agriculture Organization of the United Nations and World Health Organization, 2006). The pathogenic mechanism of chlorpropanol on the kidney has not yet been fully elucidated. In-vivo experiments revealed that several 3-MCPD metabolites, particularly β-chloraldehyde, which is generated by the enzyme alcohol dehydrogenase, can inhibit the glycolysis enzymes glyceraldehyde 3-phosphate dehydrogenase and propanose triphosphate isomerase. Several scholars have hypothesized accordingly that the damage induced by inhibition of the glycolytic pathway and energy metabolism may be the origin of the nephrotoxic mechanism of 3-MCPD (Sawada et al., 2016).

In addition, the accumulation of calcium oxalate crystals in the kidney due to the formation of oxalic acid and calcium salt in urine may hasten the progression of nephropathy (Jones et al., 1981; Corley et al., 2005). In a rat model, the relative weight of the kidney increased when the dose of 3-MCPD reached 30 mg/kg·bw/day; rats with renal damage had oxalate crystals, namely the metabolite of 3-MCPD, accumulated on the inner membrane of the tubules as well (Ge et al., 2014). Galactosyl glycerol concentration is a preliminary indicator of 3-MCPD effects on the body. It was discovered that the amount of galactose-based glycerol in rats' urine increased after 40 days of treatment with 30 mg/kg·bw/day of 3-MCPD. It was speculated accordingly that 3-MCPD causes imbalance of β-galactosidase (β-Gal) in the kidney and epididymis, reducing hydrolyzed galactosyl glycerol to galactosyl and glycerol (Li et al., 2010).

According to other animal experiments, chloropropanols are hazardous to a variety of organs including the heart, liver, immune system, neurological system, and reproductive system. There is, however, no conclusive proof that chloropropanols have a direct toxicological effect on humans, necessitating additional study.

Formation mechanism

At present, the precise formation mechanism of chloropropanols is not known. As a result, it is not yet possible to explain the differences in their levels in food. The two classifications of potential chloropropanol formation mechanisms in food matrices are shown in Fig. 2 and Fig. 3. The first is formed during the heat-treatment process from reactions of intrinsic or added components (e.g., glycerol, allyl alcohol,

Table 1
Provisions of GEs, 3-MCPD and 3-MCPD ester in food.

Authority	Food type	Analytes	Limit requirements
SB 10338–2000	HVP, soy sauce	3-MCPD	≤ 1 mg/kg
EU (2001)	HVP, Soy sauce juice	3-MCPD	≤ 0.02 mg/kg
FAO /WHO (2001)	Food	3-MPCD	2 μg/kg
GB 2717–2003	Brewing soy sauce	3-MCPD	≤ 0.02 mg/kg
EU (EC1881-2006)	HVP	3-MCPD	≤ 0.02 mg/kg
United States	HVP, Soy sauce juice	3-MCPD	≤ 1 mg/kg
AOCS	Edible oil for food processing	3-MCPD ester	< 2 mg/kg
	Edible oil (baby food)		< 0.5 mg/kg
GB 2762–2017	HVP	3-MCPD	Liquid condiment ≤ 0.4 mg/ kg Solid condiment ≤ 1.0 mg/kg
EU (2018/290)	Powdered infant milk powder	3-MCPD and esters (GEs)	125 μg/kg (50 μg/kg)
	Liquid infant milk powder	3-MCPD and esters (GEs)	15 μg/kg (6 μg/kg)
EU (2020/1322)	Fish oil and other Marine bio fats	Glycidyl esters (GEs)	1000 μg/kg
	Marine bio fats (baby food)		500 μg/kg
	Powdered infant formula		50 μg/kg
	Vegetable oils and mixed vegetable oils	3-MCPD and 3-MCPD ester	1250 μg/kg
	Vegetable oils and fats (baby food)		750 μg/kg

Note: SB, Provincial Standard; HVP, acid-hydrolyzed vegetable protein; EU, European Union; FAO/WHO, Food and Agriculture Organization/World Health Organization; GB, National Standard; AOCS, American Oil Chemists Society; 3-MCPD, 3-monochloropropane-1,2-diol; 3-MCPD ester, 3-monochloropropane-1,2-diol ester; GEs, glycidyl esters.

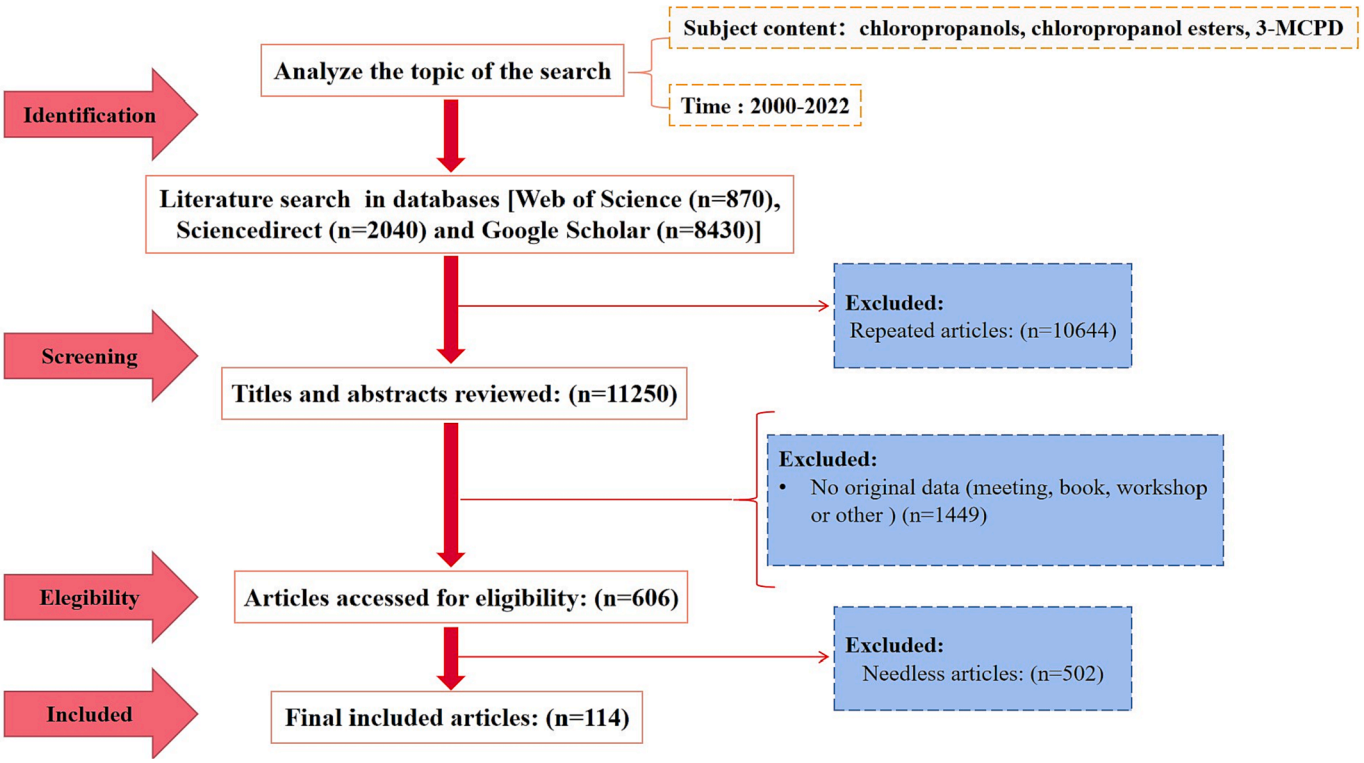

Fig. 1. Flow diagram of literature search and data collection.

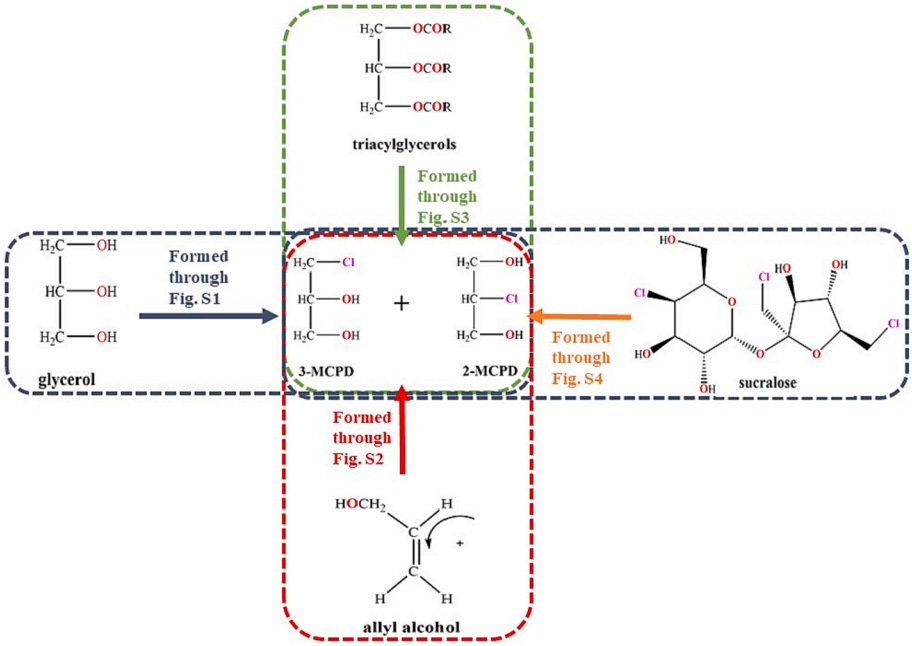

Fig. 2. Inner formation mechanism of chloropropanols and chloropropanols esters.

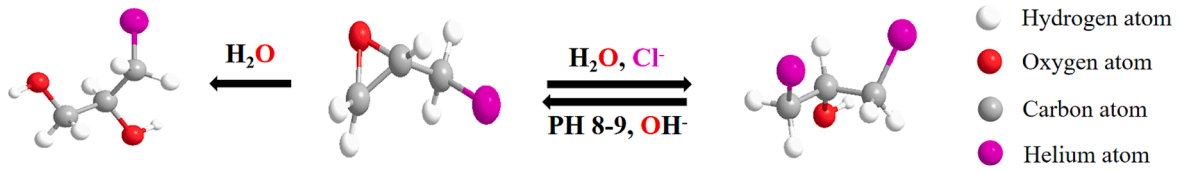

Fig. 3. External formation mechanism of chloropropanols.

chloropropanol esters, sucralose, or carbohydrates); the second is caused by the migration of chloropropanols from food packaging or contact materials to food (e.g., paper packing materials). Compared to the other three chloropropanols, 3-MCPD is the most thoroughly investigated model accompanying the clearest understanding of the formation mechanism from food matrices. 3-MCPD is used as an example in the remainder of this review.

4.1. Inner synthesis in mixed foodstuffs

The inner synthesis mechanisms of chloropropanols in foods are affected by many factors, including possible precursors, chloride anion concentrations (which may occur naturally or be added as sodium chloride), cooking methods, and oil-refining conditions. Over the last few decades, various possible precursors for chloropropanol formation have been studied including organic compounds in food (e.g., glycerol (Fig. S3), allyl alcohol (Fig. S4), chloropropanol esters (Fig. S5), sucralose (Fig. S6), and carbohydrates). Propylene glycol and glycerol are frequently used as humectants and flavor carriers in foods such as confectionery items, dried fruits, and vegetables. They are also potential precursors of chloropropanols (Wenzl et al., 2007). Collier et al. (1991) elucidated the formation mechanism by which 3-MCPD is produced in aqueous systems using glycerol and hydrochloric acid (Fig. S3). This process most likely involves a nucleophilic substitution reaction (S_N2) of the chloride anion (Collier et al., 1991). The production of chloropropanols has also been attributed to allyl alcohol, a very unstable enol structure molecule that results from the heat degradation of alliin (originally discovered in garlic) (Myszkowski and Zielinski, 1965; Kubec et al., 1997). Across thermal degradation pathways, sucralose, a common non-caloric artificial sweetener used in high-temperature bakery items, can emit hydrogen chloride at concentrations between 300 and 600 ppm (Chapello, 1998; Goldsmith and Merkel, 2001). Under pyrolytic conditions, the produced hydrogen chloride in these products can react with glycerol to produce various monoesters of chloropropanols, which may then rapidly transform into their corresponding di-esters (Rahn and Yaylayan, 2010). Chloropropanols can also be produced by degrading their esters.

The temperature of food thermal process is also a very important factor affecting the formation of chloropropanol and their fatty esters. Normally, chloropropanols are formed during the thermal process of various foodstuffs above 150 ℃ (Wenzl et al. 2007). For chloropropanol fatty esters, their formation mechanisms are quite complex and research results are inconsistent. Firstly, the 3-MCPD ester content of fried potato chips decreased with the increase of frying time, but increased with the increase of frying temperature (Yu et al., 2017a; Yu et al., 2017b). In another study for deep-fat frying of chicken breast meat samples, there was a significant (p less than 0.05) decrease in the 3-MCPD esters with the increasing of the frying duration. While, the 3-MCPD esters were decomposed and their levels were lower at high temperature when heated for 5 days (Yu et al., 2017a; Yu et al., 2017b). In a previous study, the amount of 3-MCPD esters decreased with increasing temperature over the range 100–230 °C and reached its highest value at 100 °C (Svejkovsk and Dole, 2006). While, in another study, the amount of 3-MCPD esters reached their highest values within 1–1.5 h at 220–260 °C (deodorizing period) based on the lab-scale physical refining, and then their decomposition rate increased with the increasing temperature (Li C. et al., 2016).

The concentrations of 3-MCPD esters and 3-MCPD in Chinese dishes were identified as 516.11 μg/kg and 17.88 μg/kg in restaurants and 75.86 μg/kg and 10.43 μg/kg in school canteens, respectively. These concentrations were found to differ significantly with different cooking methods. In decreasing order of intensity, the following cooking techniques have the most significant effects on the productions of 3-MCPD and its esters: deep frying > griddling > stir frying > braising > stewing (Zhang J.L. et al., 2020). Throughout the oil-refining process, the synthesis of chloropropanol esters, as the primary precursor for chloropropanols, is affected by triglyceride type, chlorinated compounds, acidity of the oil, metal ions, water dosage, and deodorization temperature (Liu Z. et al., 2022; Silva et al., 2019; Ramli et al., 2020; Zhang et al., 2021; Lakshmanan and Yung, 2021; Gao et al., 2022).

Recently, chloropropanol esters have attracted much attention due to their ubiquity and high levels in refined edible oil products. Although, there is no direct evidence to support any adverse health effects from chloropropanol esters, they have raised concerns due to their ease of hydrolysis to free chloropropanol in the gastrointestinal tract and the large amount of processed vegetable oil in many different foods. The data is fragmented and the major pathways of chloropropanol formation in food from ester hydrolysis remain unclear. The formation mechanisms under discussion presently, and the reactions that have been observed to date, are shown in Fig. S7.

The formation mechanisms of chloropropanols in foods have been postulated via three viable synthesis pathways with chloropropanol esters as potential formation precursors: (i) direct nucleophilic attack by the chloride ions at the carbon atoms of glycerol with ester or protonated hydroxyl groups (Fig. S7a and Fig. S7b); (ii) nucleophilic attack by chloride ions with the formation of reactive intermediates (e.g., acyl oxonium ions or an epoxide ring in the form of glycidol) prior to the attack (Fig. S7c); and (iii) free radical reaction via the formation of radicals as a reactive intermediate, which are formed by glycerol ester (Fig. S7d) (Hamlet et al., 2011). Shimizu et al. (2012) identified monoglyceride (MAG) as the most active potential precursor for 3-MCPD through a simulated deodorization experiment with acylglycerol and chlorine salt as substrates. Smidrkal et al. (2016) found that when the level of free fatty acids in sunflower oil refining is the same as that of 3-MCPD ester, diglyceride (DAG) is more likely to produce 3-MCPD than MAG. The various experimental model systems utilized in the research process may be the cause of this dispute.

4.2. External contamination via migration

3-MCPD and 1, 3-DCP have been detected in paperboard packaging (Devore et al., 1991; Boden et al., 1997) as by-products of wet-strength additives. Polyamidoamine-epichlorohydrin (PAE) is the predominant wet-strength additive used for moisture resistance in paper products. The proposed mechanism through which chloropropanols originate in this type of packaging are shown in Fig. 3(Peng et al., 2017). In water, the hydrolysis of epichlorohydrin produces 3-MCPD, whereas the interaction between the epoxide group of epichlorohydrin and the chlorine ion produces 1, 3-DCP. These pollutants migrate from the packaging into food products upon contact with the food matrices.

Chloropropanols are generated as food contaminants during heat-treatment via the reaction of allyl alcohol, chloropropanol esters, sucralose, carbohydrates, glycerol or propylene glycol, and chloride ions (Hamlet et al., 2002; Wenzl et al., 2007; Collier et al., 1991; Myszkowski and Zielinski, 1965; Kubec et al., 1997; Chapello, 1998; Goldsmith and Merkel, 2001; Rahn and Yaylayan, 2010). Different observations have been made regarding the synthetic paths of chloropropanols due to the different experimental models employed by researchers (Shimizu et al., 2012; Hamlet et al., 2011; Smidrkal et al., 2016). Further studies are yet needed to secure realistic experimental models.

5. Detection approaches

Approaches for the detection of chloropropanols or their corresponding esters in food matrices are a necessary first step to further research. An overview of existing detection mechanisms and approaches is given in Fig. 4 and Table S2.

5.1. Detection of chloropropanols

Existing determination methods for chloropropanols include chromatography, electro-chemical methods, and optical analysis; each have

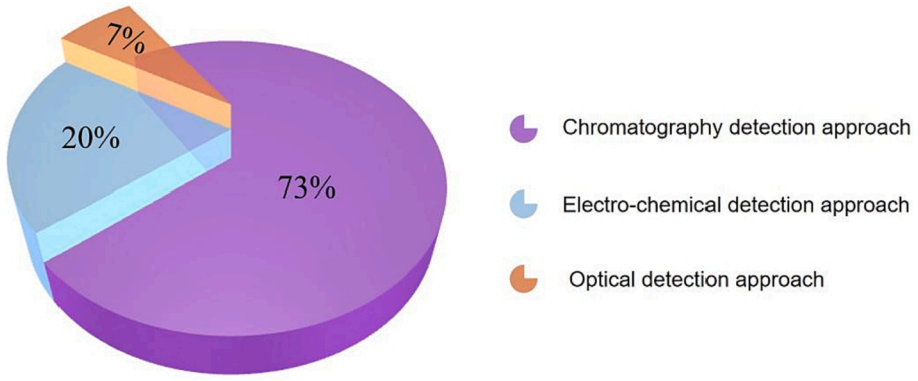

Fig. 4. Proportions of detection methods for chloropropanols.

distinct qualitative and quantitative mechanisms (Chi et al., 2022; Custodio-Mendoza et al., 2018; Li et al., 2022; Martin et al., 2021; Cheng et al., 2022; Chen et al., 2022; Nemati et al., 2021; Yaman et al., 2021; Zhao et al., 2012).

5.1.1. *Chromatography detection approach*

HPLC, GC, and GC–MS methods are not appropriate for the detection of chloropanols due to intrinsic limitations such as molecular structure characteristics, low volatility, and low molecular weight. Researchers developed a conventional derivatization pretreatment process prior to GC analysis, which effectively circumvented these restrictions. Derivatization pretreatment can produce more volatile analytes to prevent undesired interactions of chloropropanols with other components during sample preparation and GC analysis. By derivatization, a variety of analytical methods have been established for determinations including GC (Plantinga et al., 1991), GC–MS (Mezouari et al., 2015), and HPLC coupled with fluorescence detection (FLD) (He et al., 2021), as shown in Table S2.

Derivatization reagents are the most crucial factors during analysis processing. The most popular ones for detecting chloropropanols are heptafluorobutyrylimidazole (HFBI), heptafluorobutyric acid (HFBA) (Abu-El-Haj et al., 2007), phenylboronic acid (PBA) (Huang et al., 2005), and butaneboronic acid (BBA) (Pesselman and Feit, 1988; Retho and Blanchard, 2005; Cao et al., 2009). With a detection limit (LOD) of less than 1 μg/mL, Schurig and Wistuba (1984) successfully identified 3-MCPD in an acid-hydrolyzed vegetable protein for the first time by GC in 1984. Later, Pesselman and Feit (1988) improved the method's detection sensitivity by ten orders of magnitude and further developed it toward an LOD of 0.10 μg/mL (S/N = 3). However, the structural characteristics of chloropropanols lead to unfavorable interactions with components in the GC system, resulting in poor peak shape and low sensitivity. Relying solely on residence duration for qualitative identification of target residues is unreliable as well (Gao et al., 2006).

A combination of GC and MS can be used to determine chloropropanol concentrations at a parts-*per*-billion (μg/kg) level of 3-MCPD in HVP, flour, bread, and other products with LOD below 3–5 μg/kg (Hamlet and Sutton, 1997). The Association of Official Analytical Chemists (AOAC) published a method for qualitative and quantitative determination of 3-MCPD in foods by GC–MS with LOD of 0.005 mg/kg (Brereton et al., 2001). In June of 2017, GC–MS was also defined by Chinese professionals as an important method in "National food safety standard determination of chloropropanols and fatty acid esters in food" with the LOD of 3-MCPD as 0.005 mg/kg (GB5009.191-2016, China). Prior to HPLC-FLD, a derivational pretreatment method by high-acid oxidation was developed with LOD of 0.36 ng/mL for the quantitative detection of 3-MCPD in vegetable oil and water samples (Hu et al., 2013). The essence of this approach is the generation of chloroacetaldehyde via the oxidization cleavage of 3-MCPD with sodium periodate. HPLC analysis coupled with an FLD detector can be used as a monitor after fluorescence derivatization with adenine. Compared to the GC–MS method, this method has a lower LOD (by about 10 orders of magnitude) without any complex pretreatment, extraction, or enrichment measures required. The average recovery of all measured values was 95.36 % in a relevant study, and the relative standard deviation (RSD) of repeated measurement was less than 3.44 % indicating excellent accuracy and sensitivity of this method.

Several other pretreatment approaches for the detection of chloropropanols have been proposed as well, such as the molecular imprinted polymer (MIP) membrane extraction with GC–MS (Qiu et al., 2018), ultrahigh-performance liquid chromatography, and microwave-assisted derivatization (MAD) with HPLC-UV (Chung et al., 2018). These methods are versatile, as they apply over a wide range of samples; they are also efficient and sensitive enough for detection limits of ppm or ppb levels. However, they require expensive instruments and time-consuming experimental procedures. Further, because all of the extract's nucleophilic chemicals can react with the derivatization reagents, these methods lead to excessive background noise, poor selectivity, and low content of the distinctive ions. HFBI is also highly sensitive to moisture, which complicates the consistent derivatization process.

5.1.2. *Electro-chemical detection approach*

In a study by Sun et al. (2014), an electrochemical approach was established based on an electrochemical sensor obtained from a glassy carbon electrode (AuNP/GCE) enhanced with gold nanoparticles and coated with a MIP film. In order to detect 3-MCPD in soy sauce samples, potassium ferricyanide and potassium ferrocyanide ($[Fe(CN)_6]^{3-/4-}$) were used as probes (Sun et al., 2014). The LOD of this method is 3.8×10^{-18} mol/L and the average recovery rate of 3-MCPD ranges from 95.0 % to 106.4 % (RSD less than 3.49 %), indicating strong adsorption performance and selectivity. However, the complexity of the sensor's synthesis process and the number of repeated applications restrict the scope of its application.

Yuan and coworkers developed a method that immobilizes hemoglobin (Hb) using magnetic molecular imprinted nano-polymer and uses Hb's reducibility to detect 3-MCPD with an LOD of 0.25 mg/L (Yuan, et al., 2019). The qualitative principle of this method is a reduction peak current at −0.236 V, which can be electrochemically produced and reduced by 3-MCPD through Hb catalysis; the quantitative principle is an increase in the reduction peak intensity with increase in 3-MCPD concentration at the given current. Its RSD is 2.9 %. Drawbacks to this approach include need to add nitrogen to the electrolyte during the detection process and the limited shelf life of the modified electrode.

5.1.3. *Optical detection approach*

A detection method for 3-MCPD in soy sauce was developed based on fluorescence with a molecule-imprinted template on a paper substrate, where samples can be directly analyzed without pretreatment (Fang et al., 2018) (Table S2). The LOD, recovery, and RSD of the method are

0.6 ng/mL, 97.2 % ~ 105.3 %, and less than 5.6 %, respectively, indicating higher accuracy than the HPLC-FLD approach. In addition, the HPLC-FLD method requires complex sample pretreatments (oxidation cleavage and derivatization of the samples), and it is likely that incomplete conversion impacts the outcomes of the process according to its 98.96 % conversion rate. Drawbacks to the fluorescence method include the poor mechanical stability of the paper substrate and the time-consuming surface modification procedure.

In addition to the methods discussed above, several other approaches have been developed for chloropropanol detection (e.g., UV–vis spectroscopic techniques) (Aama et al., 2020) each with their own advantages and disadvantages.

5.2. Detection of chloropropanol esters

Following ester hydrolysis and transesterification, free 3-MCPD or 2-MCPD is typically measured indirectly to determine the presence of chloropropanol esters in foodstuffs (Chung and Chan, 2012; Chai et al., 2016; Dubois et al., 2019; Garballo-Rubio et al., 2017; Hidalgo-Ruiz et al., 2021; Ioime et al., 2021; Karl et al., 2016; Liu et al., 2013; Marc et al., 2016; Samaras et al., 2016; Wang et al., 2016; Yamazaki et al., 2013; Zheng et al., 2021; Li et al., 2015; Li et al., 2020) (Table S2). These methods typically include two steps: first, the release of free 3-MCPD from its esterified form, and second, the detection of free 3-MCPD (Zheng et al., 2021). However, the possible formation of additional 3-MCPD from ester hydrolysis during the pretreatment can produce positive-biased results. Some other esters can undergo alkaline or acidic catalyzed transesterification and transform into 3-MCPD (Chai et al., 2016).

Researchers have developed several other detection techniques for chloropropanol esters that do not necessitate hydrolysis pretreatment in response to the unreliability of the methods discussed above. Katsuhito Hori et al. (2012) developed a technique with LOD less than 0.063 mg/kg for measuring 3-MCPD ester in edible oil via supercritical fluid chromatography (SFC) coupled with triple quadrupole mass spectrometry (QqQ-MS). SFC, as a novel separation method, was employed for the analysis of 3-MCPD esters; it is suitable for the analysis of hydrophobic compounds due to the polarity of the supercritical fluids. (For instance, carbon dioxide is compatible with hexane.) This was the first report on the analysis of 3-MCPD esters by SFC/QqQ-MS. In another study also by Katsuhito Hori et al. (Hori et al., 2012), a method for the detection of 3-MCPD esters and GEs in edible oil using liquid chromatography time-of-flight mass spectrometry (LC/TOF-MS) was developed. For GEs, the LOD was less than 0.16 ng/kg; for 3-MCPD monoesters and di-esters, LOD was 0.86 and 0.22 ng/mL, respectively (Hori et al., 2012). Liu H.H. and coworkers (2016) reached an RSD of less than 8.1 % for the simultaneous determination of 3-MCPD esters residues in foods using solid phase extraction coupled with ultra-performance liquid chromatography-electrospray tandem mass spectrometry (UPLC-MS/MS). The detection of 2-MCPD and 3-MCPD fatty acid di-esters in edible oils was established by MacMahon and coworkers' study (2013) using electrospray ionization (ESI) liquid chromatograms combined with tandem mass spectrometry (LC-MS /MS) to a maximum limit of quantification of 30 ng/g (PPB) and RSD of 2–16 %. The deuterium internal standard substances of two esters were added to quantify them for accurate quantitation of isomeric 3-MCPD and 2-MCPD di-esters. Though these recently developed detection methods may be powerful tools for examining 3-MCPD esters, the apparatus is expensive and a large number of internal standards are required.

The most common analytical techniques for determining the presence of chloropropanols or their esters in food matrices are GC–MS or LC-MS following sample derivatization pretreatment. We expect that future research will center on determination methods with easy, convenient sample preparation and low LOD.

6. Occurrence in food

Chloropropanols, their esters, and GEs are mainly present in foodstuffs such as soy sauce, edible vegetable oil, bread, infant formula, noodles, and other products. As reported previously, the amounts of 3-MCPD, 3-MCPD esters, and GEs produced during different cooking methods vary; frying and stewing produce the highest and lowest amounts of these toxicants, respectively (Zhang et al., 2020). As shown in Table S3, the reference data for these contaminants have decreased in the past few years, indicating that additional/improved mitigation measures have effectively reduced contaminant concentrations in foodstuffs. Infant formula is currently the primary research focus.

Several reports have revealed that the concentrations of chloropropanols or their esters and GEs vary by locality (Becalski et al., 2018; Nguyen and Fromberg, 2020; Arisseto et al., 2017; Fan et al., 2021; Zhang et al., 2020; Custodio-Mendoza et al., 2019; Kamikata et al., 2019). In China, the concentrations of 3-MCPD ester and 2-MCPD ester range from ND to 1.469 mg/kg and ND to 0.218 mg/kg, respectively (Cui et al., 2021). In the United States, concentrations for bound 3-MCPD and glycidol in infant formulas containing palm/palm olein range from 0.021 to 0.92 mg/kg and from < LOQ to 0.40 mg/kg, respectively; the levels in formulas without palm/palm olein range from 0.072 to 0.16 mg/kg and from 0.005 to 0.15 mg/kg, respectively (Leigh and MacMahon, 2017). The average bound 3-MCPD and bound glycidol concentrations in the U.S. infant formula collected between December 2017 and January 2019 range from 0.035 μg/g to 0.63 μg/g and from 0.019 μg/g to 0.22 μg/g, respectively (Beekman et al., 2020). In Germany, however, the average concentrations of 3-MCPD and GEs declined from 0.094 to 0.054 μg/g and from 0.010 to 0.006 μg/g, respectively, between 2015 and 2019 (Beekman et al., 2021). In 2013, the European Food Safety Authority announced that margarine and related products, as well as vegetable and animal fats, contained elevated levels of 3-MCPD (EFSA, 2013).

Dietary exposure assessments for 3-MCPD vary widely across age groups and diets. In a previous European population study, the average dietary exposure level of 3-MCPD was 0.5 to 1.5 μg/kg·bw/day for infants and adolescents versus 0.2 to 0.7 μg/kg·bw/day for people over 18 years of age (EFSA, 2016). A study conducted in Brazil showed 3-MCPD ester and GE intakes up to 5.81 and 10.46 mg/kg·bw/day, respectively, indicating a potential risk of 3-MCPD esters and GEs in the country's infant formula market. There are still potential risks of excessive intake of 3-MCPD esters and GEs in infant formula in some regions of the world. Extra care and regulatory measures are required to safeguard pediatric health.

7. Elimination methods

As discussed above, chloropropanols widely found in food products are potential carcinogens with possible adverse effects on human health. There is an urgent need to mitigate their levels in food products to ensure safety. Commonly used elimination methods mainly center on optimizing oil-refining conditions to reduce the amount of chloropropanol esters, which are the major formation precursors of chloropropanols. The introduction of acid, whether in an acid degumming step or via bleaching clay, can form chloropropanol esters especially at high temperatures (Ramli et al., 2011; Schurz, 2010; Bis et al., 2020). The formation of 3-MCPD esters or GEs is associated with triglyceride type, chlorinated compounds, oil acidity, metal ions, water dosage, and deodorization temperature during the oil-refining process. Techniques to eliminate these precursors before, during, or after the deodorization procedure have been established based on the parameters mentioned above (Silva et al., 2019; Ramli et al., 2020; Zhang et al., 2021; Lakshmanan and Yung, 2021; Gao et al., 2022). The five process parameters of water dosage, phosphoric acid dosage, degluing temperature, activation daily dose, and deodorization temperature can be fine-tuned to produce refined palm oil with the lowest possible amount of 3-MCPD ester while

ensuring the best possible quality. 3-MCPD ester can be reduced by 87.2 % from 2.9 mg/kg to 0.4 mg/kg in the conventional refining process with color and oil stability index of 2.4R and 14.3 h, respectively (Zulkurnain et al., 2013).

Silva et al. (2019) discussed the effects of single and double washing bleach steps on the levels of 3-MCPD ester and 2-MCPD ester in refined palm oil. The double washing bleach significantly reduced the levels of 3-MCPD ester, 2-MCPD ester, and GEs up to 17.1 %, 56.4 %, and 76.9 %, respectively (Silva et al., 2019). Interactions between degumming and bleaching processes, as well as their effects on the formation of 3-MCPD ester and GEs in refined, bleached, and deodorized palm oils have also been investigated; water degumming is effective in lowering the 3-MCPD ester level by up to 50 % (Sim et al., 2018). The precursors of chloropropanols should be removed or inhibited during refining to halt the synthesis of these contaminants. Controlling the synthetic precursor of chloropropanols can eliminate them during the oil-refining process.

Alternative approaches have emerged in recent decades including molecular distillation, enzymatic removal, and adsorption (Strijowski et al., 2011; Ramli et al., 2011; Ren et al., 2018; Kyselka et al., 2018). Molecular distillations are particularly successful in removing 3-MCPD ester and GEs from refined oils (Wen L. et al., 2022; Strijowski et al., 2011; Kyselka et al., 2018). An easy enzymatic method was established to convert 3-MCPD and its esters from a plant oil reaction medium to non-toxic glycerol without necessitating high temperatures or organic solvents. According to Bornscheuer and Hesseler (2010), 3-MCPD ester can be converted by an enzyme cascade into the harmless product glycerol via an enzymatic cascade reaction. Adsorption can also remove 3-MCPD ester after refining plant oil; commonly used adsorbents include zeolite, magnesium silicate, activated carbon, and active soil (Strijowski et al., 2011; Ramli et al., 2020; Ren et al., 2018; Kyselka et al., 2018; Wen L. et al., 2022). A calcinated zeolite and a synthetic magnesium silicate were shown to be able to lower the concentration of 3-MCPD esters and similar compounds by up to 40 %, according to a study by Strijowski (2011). The zeolite in particular was able to reduce the content of 3-MCPD esters and associated compounds relatively quickly in a wide variety of treatment temperatures. In a different study by Wen (2022), the 3-MCPD esters were removed during the decolorization step of the tea oil refining process using four adsorbents, including bleaching clay, powdered activated carbon, rod-like activated carbon, and magnesium silicate. As a result of the 2 % increase in magnesium silicate addition, the content of 3-MCPD esters in camellia oil decreased first, reaching its lowest level of 4.10 mg/kg, and the related adsorption rate increased to 42.4 %. While, activated clay has the most effective adsorption in a different study for the process of refining fish oil (Gong S. S. et al., 2018). Therefore, further research is required on the adsorption impact caused by adsorbent surface area, pore structure, and surface chemical composition.

We expect that future research will center on pursuing more efficient, affordable ways to manage the levels of chloropropanols and their esters in food products without the introduction of secondary pollutants.

8. Conclusion

Chloropropanols and their esters or GEs are food contaminants of various toxicities that may critically affect food safety. This paper provided a review of the formation, detection, and removal of chloropropanols and related esters. The formation processes were initially separated into internal and exterior categories, with precursors including allyl alcohol, chloropropanol esters, sucralose, carbohydrates, glycerol, or propylene glycol. The factors that affect chloropropanol formation in cooking oils and other food products with complex substrates require further study, as it is evident that chloropropanols are easily generated in foodstuffs and inevitably ingested. At present, GC–MS and LC-MS with sample derivatization pretreatment are the most common analytical methods of chloropropanols and their esters in food matrices. There has been an overall reduction in the past five years of chloropropanols, their esters, and GEs in foods. Apart from infant formula sold in Brazil, humans have a generally low risk of exposure for chloropropanol esters and GEs. However, recent restrictions on 3-MCPD and its fatty acid esters defined by the standard Commission Regulation (EU) 2020/1322 show that additional risk evaluation is still required for certain populations, including newborns and young children (EC, 2020).

The removal of carcinogenic chloropropanol formation precursors may reduce their levels in certain foods. Future research on chloropropanols, their esters, and GEs may center on developing more practical experimental models of the formation mechanism, easier-to-use sample preparation techniques, low-LOD testing methods, and more efficient and affordable elimination techniques. Tackling unresolved issues will mitigate existing uncertainties concerning chloropropanols and their esters as they affect human health.

CRediT authorship contribution statement

Changxia Sun: Writing – original draft, Conceptualization. **Ni Wu:** Software, Data curation. **Shunli Kou:** Supervision. **Haolin Wu:** Methodology. **Yu Liu:** Formal analysis. **Annan Pei:** Resources. **Qiang Li:** Project administration, Visualization, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

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