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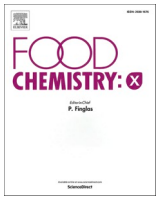

4-Methylimidazole, a carcinogenic component in food, amount, methods used for measurement; a systematic review

Nader Akbari [a], Hamed Shafaroodi [b], Mahdi Jahanbakhsh [a], Samireh Sabah [c], Ebrahim Molaee- aghaee [a], Parisa Sadighara [a,*]

[a] Department of Environmental Health, Food Safety Division, Faculty of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Food and Drug Administration, Ministry of Health and Medical Education, Tehran, Iran

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ABSTRACT

4-methylimidazole (4-MEI) is widely used industrially. This carcinogenic component has been reported in some types of food. It is usually produced by the caramelization process in food, drinks and caramel coloring. The possible mechanism for the formation of this compound in food is the Maillard reaction. In order to estimate the amount of substance 4-MEI in food, a systematic study was conducted. The selected keywords were 4-methylimidazole, 4-MEI, beverage, drink, meat, milk, and coffee. 144 articles were obtained from the initial search. The articles were evaluated and finally, the data of 15 manuscripts were extracted. Based on the data extracted from selected articles, the highest amount is reported in caramel color, coffee, and cola drinks. In 70% of the selected studies, the analytical method was based on liquid chromatography. In this method, there is no need for derivatization. SPE columns were used to extract samples in most manuscripts. According to per capita consumption, the most exposure to 4-MEI is through coffee. In high risk food products, regular monitoring with analytical methods with high sensitivity is recommended. Furthermore, most of the selected studies were about the validation method, so few samples were selected. It is recommended to design more studies with a high sample size to accurately evaluate this carcinogenic compound in food.

Introduction

4-methylimidazole (4-MEI) is a heterocyclic nitrogen compound (Cunha, Senra, Cruz, Casal, & Fernandes, 2016; da Costa, Albuquerque, Costa, & Bragotto, 2023). This compound is light yellow and crystalline solid(Morita & Uneyama, 2016). Its solubility in water and alcohol is high(IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013). It is used in the manufacture of rubber, pigment and the agricultural and pharmaceutical industries(Lim & Shin, 2013). This chemical is used as a raw material for paper ink and paint(Chan, Hills, Kissling, & Nyska, 2008). Furthermore, this compound is found in cigarette smoke(Petruci, Pereira, & Cardoso, 2013).

It is a carcinogenic compound. This compound prevents the activity of metabolic enzymes. It leads to liver and lung cancer (Altunay & Gürkan, 2019; Ye, Chen, & Feng, 2017). According to the classification of the Agency for research on cancer, it is in category 2B, which means it is possibly carcinogenic to humans(Cancer, 1979). In a study, rats were prescribed 170 mg of this compound per kg of their body weight per day. Neoplasia of the respiratory system was observed in both male and female mice(da Costa et al., 2023)0.4-MEI is also neurotoxic and leads to tremors and seizures(C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014). It leads to hyperexcitation in animals(Petruci et al., 2013). 4-methylimidazole has led to convulsions in some species, including mice, rabbits, cows, and chickens(Karim & Smith, 2015). Anemia was also reported in exposed rats (Lee & Lee, 2016). Furthermore, mononuclear cell leukemia was observed in exposed female rats(Chan et al., 2008). According to the Office of Environmental Health Hazard Assessment, the limit of a person's daily intake is 16 Âµg(Kim et al., 2013).

4-MEI is reported in some foods containing caramel or caramel color (Cunha et al., 2016). 80% of the colors used in the food industry belong to caramel(Karim & Smith, 2015).Caramel is divided into four types. The first type is plain caramel, the second type is sulfite caramel, the third type is ammonia caramel, and the fourth type is ammonia sulfite caramel(C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014). The first type is added to food as a flavoring and the other three types as color

* Corresponding author.
E-mail address: sadighara@farabi.tums.ac.ir (P. Sadighara).

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(C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014). The third type, caramel color produced from ammonia compounds, is widely used in the food industry (Ye et al., 2017). Cola soft drink, which is one of the most popular drinks in the world, has a caramel color. The third type and the fourth type contain the carcinogenic compound 4-methylimidazole (C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014). The permissible limit for this combination in caramel colors is 200 mg/kg (Petruci et al., 2013). The Codex Alimentarius has allowed 250 mg/kg (Wieczorek, Przygoński, & Jeleń, 2018). Therefore, one of the common exposures to 4-methylimidazole is cola drinks.

It is known as one of the possible mechanisms of its formation in food due to the Maillard reaction reaction(S. Hyong, M. Chu, H. Park, J. Park, & K. G. Lee, 2021). Its formation in food happens due to the combination of carbohydrates and nitrogenous compounds(Akbari-Adergani, Ahmadi, Jahedkhanki, Nodehi, & Sadighara, 2020; Chen, Yan, Lv, Zhao, & Wu, 2018).Therefore, 4-methylimidazole is formed in foods that have high carbohydrates and nitrogenous compounds due to heat (C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014; D. E. Folmer, D. L. Doell, H. S. Lee, G. O. Noonan, & S. E. Carberry, 2018). This compound is also formed when green coffee beans are roasted. Furthermore, a significant amount has also been detected in meats after 60 min of cooking(Wang et al., 2021). In general, it is found in food in two ways, one by heat and the other by the addition of caramel color (D. E. Folmer, D. L. Doell, H. S. Lee, G. O. Noonan, & S. E. Carberry, 2018). The most exposure is due to the addition of caramel color (D. E. Folmer, D. L. Doell, H. S. Lee, G. O. Noonan, & S. E. Carberry, 2018). In this systematic study, the reported amount of this neurogenic and carcinogenic compound in various foods was investigated. Foods that have the highest amount of this compound are explained along with the reasons. Moreover, the analytical methods to measure it in food and prepare food samples were discussed.

Method

This study was based on the Prisma checklist. Each procedure was performed by two team members to prevent bias. The disagreements were reviewed by the corresponding author.

The search process

At first, it was checked in different databases that no systematic study has been published in this regard. In the next stage, the keywords were selected. The selected keywords were selected by preliminary review of the texts in the form of (4-methylimidazole or 4-MEI) and (beverage or drink or meat or milk or coffee). Three databases, PubMed, Science Direct and Scopus, were selected for search. The search was done on January 29, 2023. This part of the research was done by two of the authors (N.A and H. SH).

Inclusion and exclusion of study

The time limit for searching was not applied as a criterion for the exclusion of manuscripts in this study. The inclusion criteria of this study included studies that measured the composition of 4-MEI in various types of food. Wine and alcoholic beverages were excluded. Manuscripts that did not declare the mean or SD were excluded from the study at the full-text review stage. Furthermore, review studies, experimental studies on animals and non-English language studies were excluded from this study.

Result

The search results in databases

144 articles were obtained by searching the databases. Duplicate articles were removed. The articles were initially evaluated by carefully reading the title and abstract. After initial evaluation, 46 articles were selected for full review. The full text of manuscripts that were not available were emailed to the corresponding author. The quality assessment of the articles was based on 5 points. The articles that got the required score (3 or more than 3) were included in the study. 5 points included these factors: the clarity of the details of the 4-methyl measurement method, the measurement of 4-MEI with a valid method, considering the confounding factors, the number of significant sample sizes and declaring the mean and standard deviation. The manuscript that the number of tested samples was one were excluded from the study. Some articles were based on the development method and were not measured on real samples and were excluded from the study. The search process can be seen in Fig. 1.

The data extracted for table

In this research, after initial and quality evaluations, 15 articles were selected for data extraction. The name of the first author, the year of publication of the manuscript, the country, the amount and number of samples, the type of food, the method of extracting and preparing the sample, and analysis device were extracted from the articles and summarized in Table 1. Most of the research in this field was done in China and then in Korea.

Discussion

In this study, based on the extracted data, compound 4-MEI is reported in food products, which include various types of drinks and sauces, vinegar, coffee and tea, meat, and caramel color. The highest amount was reported in the third and fourth types of caramel colors (Petruci et al., 2013). According to the formation mechanism of this dangerous compound, which is caused by the caramelization process, this observed amount is expected. In the case of meat, it is probably created during cooking. A significant amount was reported in cooked meats(Karim & Smith, 2015). In a study, the amount of this compound in raw meat was reported to be zero(Fierens, Van Holderbeke, Cornelis, Jacobs, Sioen, De Maeyer, et al., 2018). Therefore, the cooking process can be effective in the formation of this composition in meats. Precursors of the Maillard reaction are produced from the hydrolysis of meat protein during cooking(Li, Tang, Wu, & Yu, 2021). It has been confirmed that this compound is a by-product during cooking or caramelization in some food products(Morita & Uneyama, 2016). In a survey, the amount measured in the meats was very different. It was reported between 41 and 1015 μg/kg(Karim & Smith, 2015). The larger amount was due to the addition of caramel to the meat, which subsequently confirms the hypothesis of the formation of this compound due to caramelization.

One of the foods that have significant amounts of 4-MEI are beverages containing cola color (Cho, Shin, Seo, Lee, Yoo, Yoon, et al., 2015; Choi & Jung, 2017; Xu, Liu, Zhao, Yu, & Zhao, 2015). In a study conducted in Belgium. The most exposure to 4-MEI is through coffee, soft drinks and beer(Fierens et al., 2018). In the Wang/2012 study, dark and light drinks were evaluated simultaneously. In the light drink, 4-MEI was not detected, but in the dark drink, a mean value of 428.5 ng/ml was detected [19]. In this research, dark drinks had caramel color. Similar to the results of this research, the results of Lim/2013 research reported an average level of 277 μg/L in cola drinks(Lim & Shin, 2013). In Goscinny/2014, the amount of 4-MEI was evaluated in cola and energy drinks. Significant amounts were detected in cola drinks, while amounts lower than LOQ were detected in most energy drinks (Goscinny, Hanot, Trabelsi, & Van Loco, 2014). In this work, the components of energy drinks are not mentioned, but caramel is mentioned on the label of these drinks. Probably the amount of caramel is not high. In another study, 4-MEI was not detected in most energy drink samples (Cunha, Barrado, Faria, & Fernandes, 2011). Caffeine is one of the components of energy drinks(Yusupova & Firdavs, 2022). Minerals, taurine, glucose glucuronolactone, and vitamins are other components of energy drinks(Leśniewicz, Grzesiak, Żyrnicki, & Borkowska-

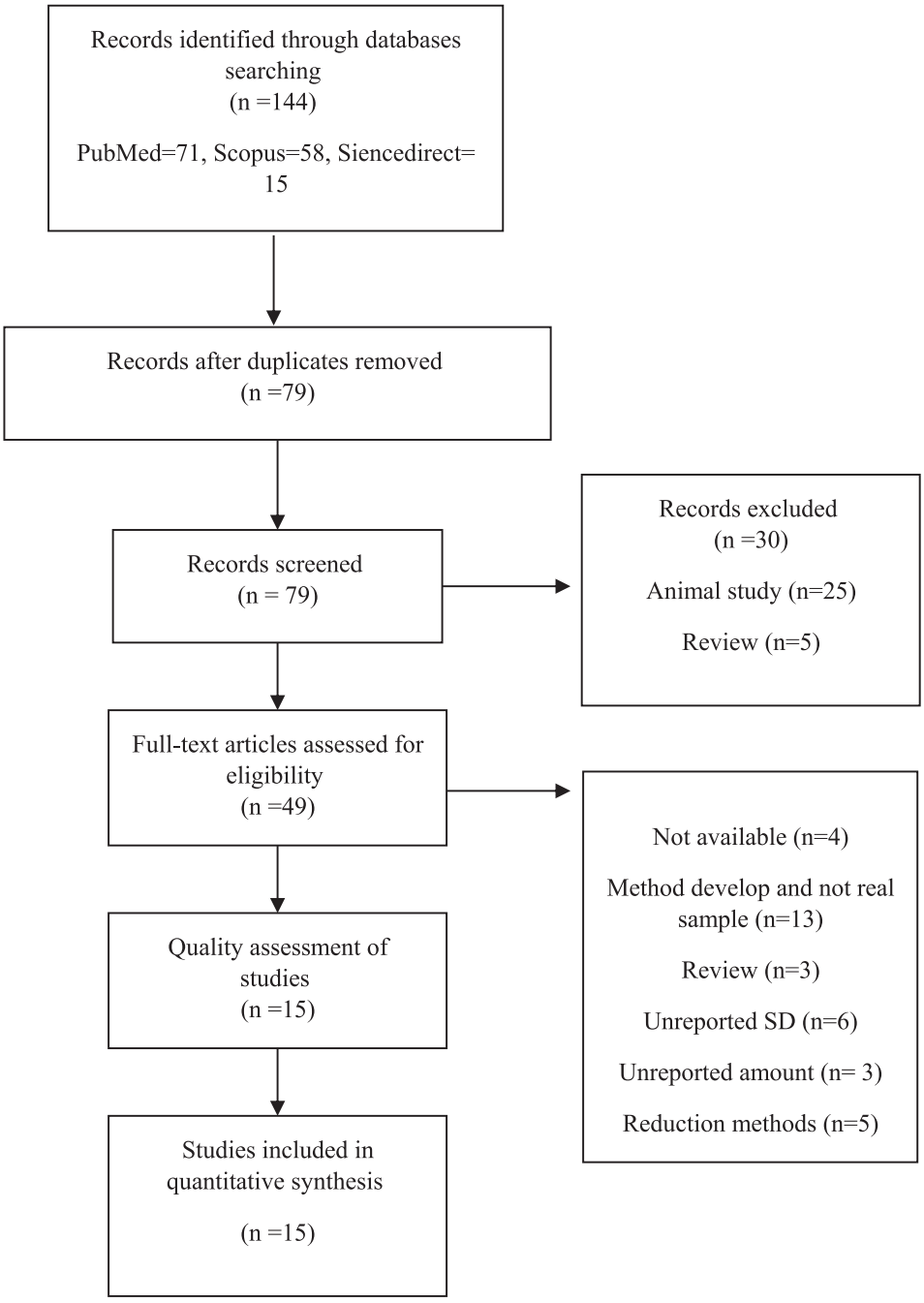

Fig. 1. The diagram of study.

Burnecka, 2016; Mora-Rodriguez & Pallares, 2014). Probably, these components do not play a role in the production of 4-MEI compound. In the study of Tzatzarakis/2017, relatively small amounts were also detected in energy drinks (Tzatzarakis et al., 2017).

Based on the extracted data, two studies have been conducted on caramel colors (Petruci et al., 2013; X. Wu, Huang, Yu, & Kong, 2016). The results of the studies are similar and the ranges of the obtained numbers are almost at the same level. This compound was not detected in the caramel color of category one, but it was detected in categories III and IV (Table 1).

Two studies have been conducted on tea, and different amounts were seen among the tested samples (Chen et al., 2018; C. Wu, Wang, Li, & Yu, 2019). This difference is caused by the production process. Tea is one of the most common drinks around the world, which has different types. The most common teas are black, green and red tea(Kumar, Kaur, Tanwar, Goyal, Gat, Kumar et al., 2018). During the black tea production process, roasting plays an important role in creating flavor in tea (Jiang, Han, Zhu, Wan, & Zhang, 2023). In this process, the Maillard reaction occurs and the 4-MEI compound is formed due to the reaction of carbohydrates and nitrogenous compounds(Chen et al., 2018). In tea leaves, the amount of amino acids and sugar is 20–30% and 20–25% of dry weight, respectively(Yang et al., 2023). The opposite of this result was observed on red and green teas (C. Wu et al., 2019). Green tea is not subjected to roasting conditions and the steaming process is done for it (Kumar et al., 2018).

The composition of 4-MEI has also been reported in a considerable amount in sauces (Chen et al., 2018; C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014). Normally, 4-MEI in sauce and vinegar is low. But if the sauce contains caramel, the amount of this composition is significantly higher. In the study of Chen/2018, a significant difference was

Table 1
The amount of 4-MEI in various type of food according to extracted data.

Sample size Amount and type of food	Sample preparation	Analytical method	Country	Name of study
Dark carbonated beverage:428.5 ± 127.6N(dark) = 13Light carbonated beverage: NDN(light) = 4 ng/ml	The samples were sonicated before injection into the device	UHPLC-MS/MS	USA	Wang/2012
Cola:277 ± 55.1 μg/L N = 4	SPME fibers were used for extraction	LC–MS/MS	Korea	Lim/2013
Caramel color class I < LOD Caramel color class III: 163.1 ± 1.1 Caramel color class IV: 163.3 ± 2.7 mg/kg N = 3 LOD = 0.16 mg/L	The color samples were dissolved in distilled water and filtered before injection	capillary electrophoresis	Brazil	Petruci/2013
Soy sauces: 957 ± 0.032 μg/kg N = 7	The extraction was carried out with bis-2-ethylhexyl phosphate and derivatization with isobutylchloroformate (IBCF)	GC–MS	Portugal	Cunha/2014
Cola drink: 2998.8 ± 56.3 Energy drinks:ND-10.8 ng/ml N = 6	The extraction was done with methanol and the clean-up step was done with SPE	UPLC-MS/MS	France	Goscinny/2014
Cola:1,050.27 ± 38.30 Apricot drink: 166.35 ± 4.83 ng/ml	The samples were diluted with distilled water	UPLC-MS/MS	Korea	Cho/2015
Ammonia caramel: 104.75 ± 1.54 μg/g N = 3	SPE column was used	HPCEC-PAD	China	Xu/2015
Beef patty 1.015 ± 0.021 Turkey sausage patty 0.280 ± 0.007 Beef pot roast 0.176 ± 0.013 Pork gravy 0.161 ± 0.015 Beef brothb 0.140 ± 0.019 Beef gravy 0.064 ± 0.003 Pork sausage patty 0.046 ± 0.007 Beef stew 0.041 ± 0.007 mg/kg N = 3	Extraction was done with sodium acetate buffer. Then derivatization was done with IBCF	GC–MS	USA	Karim/2015
Soluble Coffee (N = 10): 202 ± 57Decaffeinated coffee (N = 8): 219 ± 62Substitutes with coffee (N = 12): 562 ± 433Substitutes without coffee (N = 15): 618 ± 319 μg/kg	Extraction was done with methanol. Then derivatization was done with BEHPA	GC–MS	Portugal	Cunha/2016
Caramel color class I = ND Caramel color class III: 179.9 ± 1.4 Caramel color class IV: 126.50 ± 1.18 mg/kg N = 3	The samples were diluted.	HPLC-MS/MS	China	Wu/2016
Cola:319 ± 20 μg/L N = 3	Derivatization was done with IBCF. Then, Extraction was done with hexane and sodium bicarbonate. The hexane phase was injected into the device	GC–MS/MS	Korea	Choi/2017
Energy drinks (N = 7): 14.6 ± 8.8Soft drinks (N = 15): 224.5 ± 174.6Vinegars (N = 12): 874.8 ± 1448.6Ammonia caramel(N = 8):518 ± 123Ammonia-sulfite caramel(N = 13):165 ± 161 ng/ml	The samples were mixed with water and centrifuged. The upper solution was injected into the device	LC-MS	Greece	Tzatzarakis/2017
Soy sauces(caramel): 3505.8 ± 24.1Soy sauce(naturally brewed): 8.7 ± 0.2Vinegar(caramel): 706.7 ± 31.2Beverage (caramel): 304.9 ± 3.3Coffee: 5869.5 ± 72.1Tea: 404.9 ± 10.8Bread (caramel): 314.2 ± 8.9 μg/kg N = 2	Extraction was done by methanol. The clean-up was done using SPE	UHPLC	China	Chen/2018
Cola (N = 3): 49.2 ± 66.6Tea (red tea) (N = 2): 20.9 ± 6.5Tea (green tea) (N = 2): 6.9 ± 1.5Coffee (beverage) (N = 4): 112.9 ± 49.8Instant coffee (N = 3): 558.6 ± 391.2 μg/L	Extraction was done by QuEChERS method. For the clean-up step, PSA was used	LC-MS/MS	China	Wu/2019
Meat prepared with brown sauce: 0.5 ± 0.1 mg/kg N = 3	The extraction was done with acetonitrile and the clean-up step was done with SPE	HPLC-MS/MS	China	Li/2021

Note: IBCF; Isobutylcholoroformate, BEHPA; bis-2-ethylhexyl phosphate, SPME; solid-phase micro-extraction, QuEChERS; quick, easy, cheap, effective, rugged, and safe, PSA; Primary secondary amine, HPCEC-PAD; high-performance cation exchange chromatography with pulsed integrated amperometric electrochemical detector, LOD; limit of determination, ND; not detected, SPE; solid phase extraction.

observed between the sauce with caramel and without it (Table 1). Furthermore, there is a significant difference in the amount of 4-MEI between vinegar with caramel and without it(Chen et al., 2018). In a study, significant amounts were found in balsamic vinegars (C. Cunha, L. Senra, J. Fernandes, & S. Cunha, 2014). Ammonia caramels are used in this product (C. Cunha, L. Senra, J. Fernandes, & S. Cunha, 2014).

Coffee is one of the most popular drinks in the world. Coffee also contains high amounts of 4-MEI (Chen et al., 2018; C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014; C. Wu et al., 2019). This compound probably increases in coffee following the Maillard reaction and during the roasting process. Following the reaction between sugar and amino acid, compound 4-MEI is formed in coffee(Cunha et al., 2016). In a study, the amount of this compound was higher in *Coffea robusta* than *Coffea arabica*(S. Hyong, M. Chu, H. Park, J. Park, & K.-G. Lee, 2021). This difference is probably related to the different compounds between these two coffees. The amount of amino acids in robusta coffee is higher than in arabica coffee. Therefore, the precursor of the Maillard reaction is more abundant in robusta coffee(S. Hyong, M. Chu, H. Park, J. Park, & K.-G. Lee, 2021). Coffee is one of the oldest drinks that is widely consumed. Therefore, it is estimated that the highest exposure to 4-MEI occurs through coffee(Daniel E Folmer, Diana L Doell, Hyoung S Lee, Gregory O Noonan, & Susan E Carberry, 2018).

In this systematic review, in addition to the general estimation of amount of this compound in food, the analysis method was also discussed. Due to the fact that this compound is carcinogenic, it is necessary to measure the actual amount in food(Jacobs, Voorspoels, Vloemans, Fierens, Van Holderbeke, Cornelis, et al., 2018). The analytical method is usually done in two ways; liquid chromatography and gas chromatography. With the validation method that was carried out in the research, both methods had the necessary sensitivity. But the GC method requires a derivatization process, which is not required in the liquid chromatography method. IBCF (isobutyl chloroformate) was mostly used for derivatization (Choi & Jung, 2017; C. Cunha, L. Senra, J. O. Fernandes, & S. C. Cunha, 2014; Karim & Smith, 2015). In almost all studies, the detector was MS or MS/MS. A lower LOD can be obtained following MS/MS(Wieczorek et al., 2018). In a study with the UHPLC-MS/MS system, the amount of 4-MEI was measured in a variety of foods. The relative recoveries were determined in the range of 94% and 114%(Jacobs et al., 2018).

In sample preparation, water, methanol and acetonitrile were used (Table 1). Considering that this compound is extremely polar(Revelou, Xagoraris, Alissandrakis, Pappas, & Tarantilis, 2021). Generally, polar solvents are needed for its extraction. SPME fibers were also used for sample preparation. In the Lim/2013 study, SPME was used to extract samples. The use of SPME has advantages, such as the use of organic solvents is minimized (Shih, Lirio, Li, Liu, & Huang, 2016). SPE columns were used for the clean-up step in foods with a complex matrix. In the case of beverages and products without complex matrix, SPE was not used. In one study, QuEChERS method was used for preparation. The trueness was reported 91–113%(C. Wu et al., 2019). Measuring 4-methylimidazole requires special equipment. Therefore, the number of examined samples in the selected manuscripts was usually low, which can be mentioned as a limitation of this systematic study.

Conclusion

In this systematic study, the amount of the carcinogenic compound 4-MEI in various foods was investigated. This compound is produced as a result of Maillard reactions in food. Sauces, vinegars, and meat containing caramel, cola drinks, caramel-colored, and coffees are among the high- risk food items. Various methods have been designed to measure this compound in food. Liquid chromatography-based methods are more common. Although the search for this study was done without time restrictions, most of the studies are related to the last ten years. It is clear that the existence of this compound was recently found. Therefore, a lot of research is necessary, especially regarding its reduction in food. Furthermore, among different food items, the permissible limit has been set for caramel colors. It is necessary to define a permissible limit for high-risk foods according to the per capita consumption.

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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