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Research Article

Cumulative Risk Assessment of Dietary Exposure to Pesticide Residues in Brown Rice (*Oryza sativa* L.) from the Three Main Rice-Growing Regions in China during 2016–2020

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The residual levels of 25 monitored pesticides in 6,229 brown rice samples obtained from the 17 provinces of the three main rice-growing regions in China during 2016–2020 were analyzed, and the cumulative risks of chronic and acute exposure to pesticides for the Chinese population were assessed. The QuEChERS extraction coupled with liquid chromatography-mass spectrometry for simultaneous determination of 25 pesticide residues in brown rice was developed and validated with good accuracy and precision (recoveries of 70%–120% and RSD ≤20%). The overall detection rate and over the maximum residue limit (MRL) rate of pesticides in brown rice decreased from 39.15% and 3.59% in 2016 to 34.11% and 1.53% in 2020, respectively. The Yangtze River basin had a higher detection rate and over MRL rate (43.14% and 2.88%, respectively) compared with the Southeast Coastal region (37.28% and 2.77%) and the Northeast Plain (11.28% and 0.17%). Isoprothiolane (13.57%) and carbendazim (8.32%) were the most frequently detected in rice samples. Pesticide residues exceeding the MRLs were found most often in triazophos (0.75%) and isocarbophos (0.51%). The risk ranking of pesticide residues based on the ranking matrix showed that carbofuran, methamidophos, and isocarbophos had the highest residual risk scores of 25.09, 25.01, and 25.00, respectively. 17.7% of rice samples contained two or more pesticide residues. The cumulative risk assessments based on the relative potency factor (RPF) approach revealed that the cumulative risks of chronic and acute dietary exposure to organophosphorus, neonicotinoid insecticides, and triazole fungicides from rice ranged from 7.43×10^{-4} to 3.36×10^{-2}, which were not considered of health concern. The study provides national-scale information on the contamination levels and health risks of pesticide residues in rice, which can help develop continuous monitoring programs for pesticide residue contamination in rice in China.

1. Introduction

Pesticides, such as insecticides and fungicides, are essential in modern agriculture to protect crops from diseases and insect pests [1]. China is one of the world's largest pesticide producers and users, with 1.5 and 4.0 times the world average, respectively [2]. China's pesticide use per hectare is about 2.5–5 times the world average [3]. With the widespread use of pesticides, pesticide residues are usually found in the environment and food products, including soil [4], irrigation water [5], vegetables [6], fruits [7], teas [8], and cereals [9]. Exposure to pesticides has been shown to cause toxic effects, including carcinogenicity [10], teratogenicity [11], and endocrine disruption [12]. Recent studies have demonstrated that general populations in Asia are ubiquitously exposed to multiple pesticides, and organophosphorus (OP), neonicotinoid (NEO), and pyrethroids (PY) insecticides are found in human urine or serum [13, 14]. Therefore, there is rising concern about the human health risks of exposure to pesticides.

The general population may be exposed to pesticides through multiple pathways, such as ingestion, inhalation, and dermal absorption, with the consumption of pesticide-contaminated foods identified as the main exposure pathway

[15]. Several risk assessments of exposure to individual pesticides in food samples have been performed based on the point estimate or probabilistic approach [16–18]. If potential exposure is below the acceptable daily intake (ADI) or an acute reference dose (ARfD), the chronic or acute risk of exposure to an individual pesticide is considered acceptable. However, because more than one pesticide is present in the same food, the cumulative effects on health from multiple pesticides have been underestimated. To address the public's concerns, the United States Environmental Protection Agency and the European Food Safety Authority (EFSA) developed methodologies to perform a cumulative risk assessment of exposure to multiple pesticides that share similar modes of action [19–21]; for example, OP and carbamate (CB) insecticides inhibit acetylcholinesterase (AChE) activity irreversibly and reversibly, respectively, resulting in acute cholinergic effects. The NEO insecticides can induce neuronal depolarization by binding to insect nicotinic acetylcholine receptors. Triazole fungicides (TFs) block the ergosterol biosynthesis in fungi and subsequently disrupt the fungal cell wall. The relative potency factor (RPF) approach is used preferentially to estimate the cumulative effects of exposure to multiple pesticides, and the toxic potency of each compound is expressed as a ratio relative to an index compound (IC) [22]. Recently, some studies based on the RPF approach have been performed to estimate the cumulative risks of dietary exposure to OPs, CBs, NEOs, PYs, and TFs from food consumption for the Brazilian [23], Spanish [24], French [25], and Chinese populations [26–28], which provide scientific reference for assessing multiple pesticides exposure and associated health effects.

Rice (*Oryza sativa* L.) is the major staple food for over half of China's population, and the stability of rice production is critical for ensuring food security in China. The Northeast Plain, the Yangtze River basin, and the Southeast Coastal region are the main rice-growing regions, accounting for nearly 98% of total national rice production in China. However, indiscriminate and excessive application of pesticides in these regions results in multiple pesticide residue contaminations in rice grain [29, 30]. The OPs were frequently detected in rice samples from China, and the detection frequency of 9 out of 15 types of OPs exceeded 50% [31]. Ma et al. [32] indicated that most rice grain from Chinese markets contained multiple NEO residues. However, compared with fruits and vegetables [26–28], only a few studies have performed cumulative risk assessments of dietary exposure to multiple pesticides in rice grain for Chinese populations. Chen et al. [33] showed that chronic cumulative exposure to 7 OPs in milled rice for Chinese children (2–7 years) slightly exceeded the ADI level, suggesting a health risk of exposure to OPs for Chinese populations; however, the cumulative risks of exposure to other pesticides, such as NEOs and TFs from rice consumption for Chinese populations are poorly understood.

In this study, the 25 commonly used pesticides in rice, including OPs, NEOs, TFs, and CBs, were monitored in China during 2016–2020, based on the survey data on pesticide use patterns in rice. The residual levels of 25 monitored pesticides in 6,229 brown rice samples obtained from the 17 provinces of the three main rice-growing regions in China and their residual risk levels were investigated. The cumulative risks of chronic and acute dietary exposure to OPs, NEOs, and TFs in brown rice for Chinese populations were assessed using the RPF approach. This study aims to provide national-scale information on the contamination levels and health risks of pesticide residues in rice to support the development of a continuous monitoring program for pesticide residue contamination in rice in China.

2. Materials and Methods

2.1. Chemicals and Reagents. Mixed standards for 25 pesticides (methamidophos, pymetrozine, nitenpyram, carbendazim, thiamethoxam, clothianidin, imidacloprid, dimethoate, acetamiprid, carbofuran, isoprocarb, chlorantraniliprole, isocarbophos, fenobucarb, azoxystrobin, triadimefon, tebuconazole, triazophos, isoprothiolane, fipronil, propiconazole, prochloraz, difenoconazole, chlorpyrifos, and buprofezin) were obtained from Alta Scientific Co., Ltd. (Tianjin, China). The QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) sorbents were purchased from ANPEL Laboratory Technologies (Shanghai, China). Acetonitrile (ACN) was obtained from Merck (Darmstadt, Germany) (HPLC-grade). Other chemical reagents were supplied by Sigma-Aldrich (St. Louis, MO, USA). The standard stock solutions were prepared at $100\,mg\,L^{-1}$ in ACN and stored at −20°C.

2.2. Sample Collection and Preparation. There were 6,229 rice samples collected from 17 provinces in the Yangtze River basin, Southeast Coastal region, and the Northeast Plain of China during 2016–2020. Detailed information is described as follows: Anhui (466), Fujian (175), Guangdong (374), Guangxi (393), Guizhou (168), Heilongjiang (870), Henan (114), Hubei (415), Hunan (730), Jilin (204), Jiangsu (507), Jiangxi (646), Sichuan (388), Yunan (248), Zhejiang (249), Chongqing (168), and Liaoning (114). The geographical locations of sampling provinces and sizes in China are shown in Figure 1. Rice samples were collected by a five-spot sampling method and oven-dried at 65°C. Dried samples were then dehulled, ground, sieved (100-mesh) and stored at −20°C for further analysis.

2.3. Analytical Procedure. The pesticide residues in rice samples were extracted and cleaned using the QuEChERS methodology according to Cui et al. [28]. Briefly, approximately 5.0 g of homogenized sample (accurate to 0.1 g) was weighed into a centrifuge tube and soaked in 20.0 ml of deionized water for 30 min. Then, each tube was extracted with 25 ml of ACN and well shaken using a high-speed disperser (T25 easy clean digital, IKA, Germany). Next, 1.0 g of NaCl and 10.0 g of anhydrous $MgSO_4$ were added, then shaken vigorously, and centrifuged for 5 min at $4,000 \times g$ (Heraeus Multifuge X1, Thermo Scientific, USA). 4.0 ml of the supernatant was transferred to a new 15 ml centrifuge tube containing 100 mg of PSA, 100 mg of C18, and 1.2 g of anhydrous $MgSO_4$. The tubes were vortexed and centrifuged

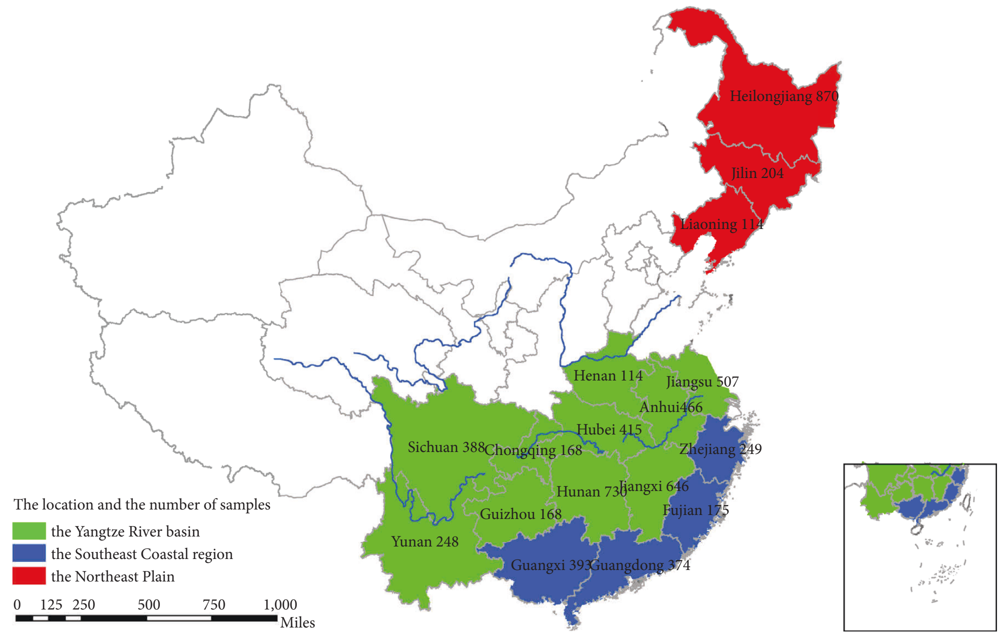

FIGURE 1: The location and the number of samples from three main rice-producing regions in China ($n = 6229$).

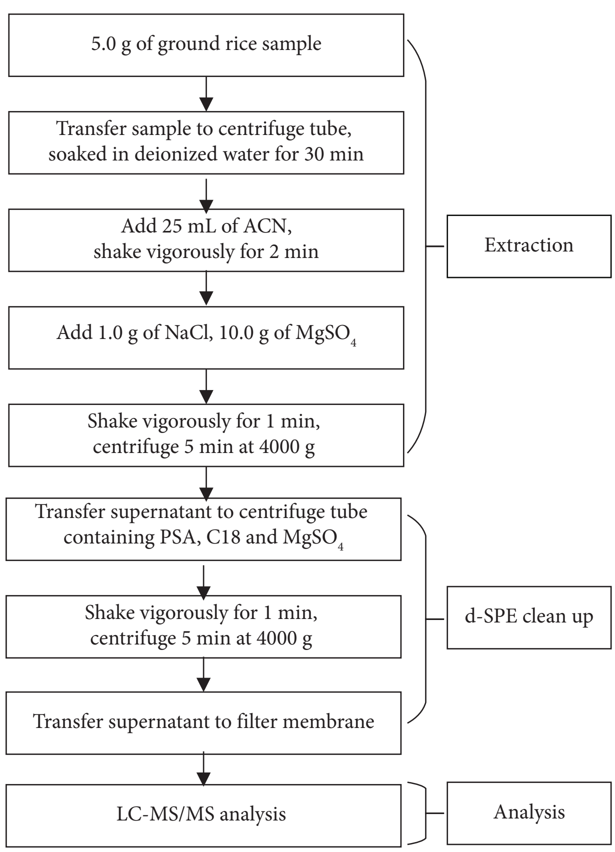

FIGURE 2: The flowchart of the analytical procedure of pesticide residues in rice samples.

for 5 min at $4,000 \times g$ (Heraeus Multifuge X1, Thermo Scientific, USA). The supernatants were filtered through a filter membrane and analyzed using an Agilent 1290 Infinity liquid chromatograph coupled to an Agilent 6,460 triple quadrupole mass spectrometer (Agilent, USA) operating in the positive ionization electrospray (ESI+) mode. The flowchart of the analytical procedure of pesticide residues in rice samples is shown in Figure 2.

The extracts were separated on a Zorbax SB-C18 column (100 mm × 2.1 mm, 1.8 μm, Agilent, USA) with 5 mM ammonium acetate containing 0.1% formic acid (mobile phase A) and ACN (mobile phase B). The flow rate was set at 0.3 ml min^{-1}, and the program was conducted as follows: 0–6 min, 20%–90% B; 6–12 min, 90% B; and 12–12.1 min, 90%–20% B. The injection volume was 0.5 μL and the column temperature was maintained at 55°C. The chromatograms of 25 pesticides in a standard mixture are shown in Figure S1, and the optimized mass spectrometric conditions and multiple reaction monitoring parameters of 25 pesticides are shown in Table S1.

The analytical method was validated according to the European Commission SANTE/12682/2019 guidelines [34].

2.4. Risk Ranking. The pesticide residual risk score was calculated using equation (1), according to the Veterinary Residues Committee of the UK [35]. The definition and individual score for each index are shown in Table S2.

$$S = (A + B) \times (C + D + E) \times F, \quad (1)$$

$$FP = \frac{N}{T} \times 100, \quad (2)$$

$$F = \frac{F1 \times 1 + F2 \times 2 + F3 \times 3}{\text{number of samples}}, \quad (3)$$

where pesticide toxicity (A) was classified into four classes according to the median lethal dose (LD50). ADIs (B) were obtained from the National Food Safety Standard of China

[36]. The proportion of rice in total dietary intake (C) is 20%–50%, according to the Dietary Guidelines for Chinese Residents 2016 [37]. Thus, the score of the proportion of rice in total dietary intake was set at 2. The frequency of a particular pesticide usage (FP, D) was calculated using equation (2), where N is the application times of pesticides during rice planting and T is the rice growth period (day). According to the Guideline for Safety Application of Pesticides (X) [38], pesticides are recommended to be used 1–3 times during the rice growth period of 120–150 days. Thus, the score of the frequency of pesticide usage was set at 0. Because there is insufficient evidence on groups with high exposure to pesticides from rice, the score of the evidence of high exposure groups (E) was set at 3. The score of the detectable residue level (F) was calculated using equation (3), where F1 is the sample number with residues detected at concentrations below the maximum residue limit (MRL), F2 is the sample number with residues detected at concentrations of 1–10 MRL, and F3 is the sample number with residues detected at concentrations ≥10 times the MRL. The residual risk score of each pesticide was ranked; the higher the score, the greater the risk.

2.5. Dietary Exposure Risk Assessment. Chronic and acute dietary exposures were performed to assess the chronic and acute dietary exposure risk, respectively, using hazard quotient (HQ) values [39].

2.5.1. Chronic Dietary Exposure Risk Assessment. The estimated daily intake (EDI) was calculated to determine chronic exposure using

$$EDI = \frac{STMR \times F}{bw}, \quad (4)$$

where STMR is the median residue (mg/kg) in brown rice (at the 50th percentile level). 100,000 Monte Carlo simulations were performed to determine the residue distribution at each percentile (P50 and P99.9) by randomly selecting one pesticide residue concentration for each sample using the risk assessment software @Risk 6.0 (Palisade Corporation, Version 4.5, Ithaca, NY, USA). The ratio F/bw is the mean rice daily intake per kilogram of body weight (g $kg.bw^{-1}$ day^{-1}) for Chinese residents, obtained from the WHO database (https://apps.who.int/foscollab/Download/DownloadConso) (Table S3). For concentrations below the limit of detection (LOD), LOD/2 was used as the concentration of each pesticide.

Chronic dietary exposure risk (HQ_c) was calculated using the following equation:

$$HQ_c = \frac{EDI}{ADI}, \quad (5)$$

where ADI (mg kg bw^{-1}) was obtained from GB 2763-2019. When $HQ_c < 1$, the chronic exposure risk is considered acceptable. Otherwise, it is considered unacceptable. The higher the HQ_c value, the greater the risk.

2.5.2. Acute Dietary Exposure Risk Assessment. The estimated short-term intake (ESTI) was used to determine acute exposure using equation (6) due to the unit weight of the edible portions of rice being lower than 25 g [40]:

$$ESTI = \frac{HR \times LP}{bw}, \quad (6)$$

where HR is the highest residue level (mg kg^{-1}) (at the 99.9th percentile level) in brown rice, and LP is a large portion, expressed as the high rice daily intake (g $kg.bw^{-1}$ day^{-1}, at the 97.5th percentile level) for Chinese residents (Table S3).

Acute dietary exposure risk (HQ_a) was calculated as follows:

$$HQ_a = \frac{ESTI}{AfRD}, \quad (7)$$

where AfRD (mg kg bw^{-1}) was obtained from the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) database [41]. The acute exposure risk is considered acceptable when $HQ_a < 1$. Otherwise, it is considered unacceptable.

2.6. Cumulative Dietary Exposure Risk. The RPF approach was adopted to assess the cumulative dietary exposure to multiple pesticides sharing similar modes of action in the same food sample. The 25 pesticides were classified into OP, NEO, TF, and CB groups. For the OP, NEO, and TF groups, RPFs were calculated based on the no observed adverse effect level (NOAEL) values of respective chronic effects on brain cholinesterase activity and hepatoxicity and respective acute effects on brain cholinesterase activity, neurotoxicity, and skeletal variations. Methamidophos, imidacloprid, and difenoconazole were chosen as the IC for OP, NEO, and TF groups, respectively. The NOAEL values were obtained from the JMPR and EFSA databases [20, 41]. Isocarbophos, nitenpyram, and the CB group (carbofuran, fenobucarb, and isoprocarb) were excluded from the RPF calculation because their NOAELs were unavailable in the above databases. The RPFs were calculated as follows:

$$RPF_j = \frac{NOAEL_{ic}}{NOAEL_j}, \quad (8)$$

where $NOAEL_{ic}$ is the NOAEL for the chronic or acute effect of the IC, $NOAEL_j$ is the NOAEL for the chronic or acute effect for pesticide j, RPF_j is the relative potency factor for pesticide j.
The cumulative risks of chronic (HI_c) and the acute dietary exposures (HI_a) for all OPs, NEOs, and TFs were calculated as follows:

$$HI_c = \frac{\sum_{j=1}^{n_j}\left(EDI_j \times RPF_j\right)}{ADI_{ic}}, \quad (9)$$

$$HI_a = \frac{\sum_{j=1}^{n_j}\left(ESTI_j \times RPF_j\right)}{ARfD_{ic}}, \quad (10)$$

where EDI_j is the EDI for pesticide j, ADI_{ic} is the ADI of the IC, $ESTI_j$ is the ESTI for pesticide j, and $ARfD_{ic}$ is the ARfD of the IC. When HI_c or $HI_a < 1$, the cumulative risk is considered acceptable. Otherwise, it is considered unacceptable.

Table 1: The method validation parameters of the 25 pesticides analyzed in this study.

Pesticide	Linearity	R^2	LOD (ng ml^{-1})	LOQ (ng ml^{-1})	Recovery[a] (%)	RSD[b] (%)
Methamidophos	$y = 1.79E+06x - 7.40E+03$	0.999	0.8	2.64	82.6	10.2
Pymetrozine	$y = 1.54E+05x - 1.13E+03$	0.999	0.5	1.65	92.4	11.3
Nitenpyram	$y = 2.05E+05x - 5.70E+02$	0.999	2.0	6.60	105.6	9.7
Carbendazim	$y = 2.83E+06x + 5.89E+04$	0.995	0.5	1.65	96.6	8.7
Thiamethoxam	$y = 1.14E+06x + 7.94E+03$	0.998	0.5	1.65	109.2	9.6
Clothianidin	$y = 3.03E+05x + 9.04E+02$	0.999	2.0	6.60	97.8	12.3
Imidacloprid	$y = 3.50E+05x - 1.00E+03$	0.999	0.9	2.97	102.8	13.1
Dimethoate	$y = 1.52E+06x + 2.46E+04$	0.998	0.5	1.65	102.6	8.5
Acetamiprid	$y = 1.45E+06x + 4.85E+04$	0.997	0.5	1.65	106.6	10.3
Carbofuran	$y = 3.68E+06x + 2.74E+04$	0.998	0.5	1.65	89.6	13.1
Isoprocarb	$y = 9.07E+05x + 1.27E+03$	0.999	0.8	2.64	103.8	9.4
Chlorantraniliprole	$y = 2.81E+05x + 6.56E+02$	0.998	3.0	9.90	98.0	13.7
Isocarbophos	$y = 4.76E+04x + 5.24E+02$	0.997	0.5	1.65	112.0	14.0
Fenobucarb	$y = 1.71E+06x - 6.20E+03$	0.999	2.0	6.60	118.0	14.1
Azoxystrobin	$y = 7.53E+06x - 1.07E+04$	0.999	0.5	1.65	112.4	6.8
Triadimefon	$y = 4.34E+05x - 3.09E+03$	0.999	0.5	1.65	90.4	10.3
Tebuconazole	$y = 6.51E+05x - 1.26E+03$	0.999	0.8	2.64	87.4	8.5
Triazophos	$y = 9.63E+06x + 2.20E+04$	0.999	0.5	1.65	106.4	11.2
Isoprothiolane	$y = 5.30E+06x - 1.23E+04$	0.999	0.5	1.65	93.0	6.2
Fipronil	$y = 7.80E+04x - 1.22E+02$	0.999	2.0	6.60	118.6	12.9
Propiconazole	$y = 8.90E+04x + 1.14E+03$	0.996	3.0	9.90	107.2	2.3
Prochloraz	$y = 1.25E+06x - 4.87E+03$	0.999	0.5	1.65	104.8	10.2
Difenoconazole	$y = 7.85E+05x - 1.42E+03$	0.999	2.0	6.60	107.0	3.4
Chlorpyrifos	$y = 5.07E+05x - 8.29E+02$	0.999	6.0	19.80	105.4	4.0
Buprofezin	$y = 9.79E+05x - 3.58E+03$	0.999	0.5	1.65	105.0	4.6

[a]The average recoveries of three spiking concentrations. [b]The average RSD of three spiking concentrations.

2.7. Statistical Analysis. Statistical analysis was done using the statistical software SPSS *versus* 19.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Method Validation. The residues of 25 pesticides in rice samples were extracted using the QuEChERS method and analyzed using liquid chromatography-tandem mass spectrometry (Table 1). Good linearity was established in the concentration range of 5–500 ng ml^{-1}, with correlation coefficients (r) of standard curves higher than 0.99. The LODs (a signal-to-noise ratio of 3 : 1) and limits of quantification (LOQs, a signal-to-noise ratio of 10 : 1) for 25 pesticides ranged from 0.5 to 6 ng ml^{-1} and 1.65 to 19.8 ng ml^{-1}, respectively. The average recoveries of all pesticides from spiked blank rice samples at the low (LOQ), middle (2 LOQ), and high concentration levels (10 LOQ) were in the range of 82.6–118.6%, with relative standard deviations (RSDs) of 0.4%–18.1%, suggesting good accuracy and precision in the applied method according to European Commission guidelines SANTE/12682/2019 (recoveries of 70%–120% and RSD ≤20%).

3.2. Pesticide Residue Levels in Different Years and Regions. A total of 6,229 rice samples were collected from the 17 provinces in the three main rice-producing regions of China during 2016–2020. Table 2 shows the variations of pesticide residue levels in brown rice samples in different years during 2016–2020. The overall detection rate was 39.15%, 36.92%, 37.94%, 32.49%, and 34.11% for 2016, 2017, 2018, 2019, and 2020, respectively, and correspondingly 3.59%, 4.04%, 1.53%, 1.18%, and 1.53% of the samples exceeded the MRLs (Table 2). The detection rate and over MRL rate remarkably decreased from 2016 to 2020, indicating that the contamination level of pesticide residues in rice grain in China declined during 2016–2020.

The regional distribution of pesticide residue levels in brown rice samples is shown in Table 3. The overall detection rate and over MRL rate in the Yangtze River basin were 43.14% and 2.88%, respectively, higher than those in the Southeast Coastal region (37.28% and 2.77%) and the Northeast Plain (11.28% and 0.17%). Moreover, there were obvious variations in pesticide residue levels in brown rice for different provinces within the same region (Table 3). For the Yangtze River basin, Jiangxi and Jiangsu provinces had the highest detection rates and over MRL rates compared with other provinces, suggesting a widespread occurrence of diseases and pests in these two areas.

3.3. Pesticide Residue Levels in Rice Samples. The 25 pesticides were detected in 6,229 rice samples. The concentrations and frequencies of detected pesticides in rice samples are listed in Table 4. The most frequently detected pesticide was isoprothiolane (13.57% of samples), followed by carbendazim (8.32%), tebuconazole (7.08%), propiconazole (5.94%), triazophos (4.61%), chlorpyrifos (4.59%), azoxystrobin (3.74%), chlorantraniliprole (2.63%), buprofezin (2.55%), and imidacloprid (1.72%). Pesticide residues exceeding the MRLs were found most frequently in triazophos

Table 2: The variations of pesticide residue levels in brown rice samples in different years in China.

Year	No. of samples analyzed	No. of samples with pesticides detected (%)	No. of samples over MRLs (%)
2016	1111	39.15	3.59
2017	1059	36.92	4.04
2018	1244	37.94	1.53
2019	1182	32.49	1.18
2020	1633	34.11	1.53

Table 3: The regional distribution of pesticide residue levels in brown rice samples in different provinces in China.

Regions	Provinces	No. of samples analyzed	No. of samples with pesticides detected (%)	No. of samples over MRLs (%)
Northeast plain	Heilongjiang	870	8.39	0.11
	Jilin	204	23.04	0.00
	Liaoning	114	12.28	0.88
Yangtze River basin	Yunan	248	79.03	0.40
	Guizhou	168	11.31	0.60
	Sichuan	388	12.37	1.29
	Chongqing	168	23.81	1.79
	Hunan	730	19.73	1.92
	Hubei	415	31.57	2.17
	Jiangxi	646	81.73	7.74
	Anhui	466	44.21	0.21
	Jiangsu	507	67.46	5.33
	Henan	114	6.14	0.00
Southeast Coastal region	Zhejiang	249	20.08	0.40
	Fujian	175	50.86	9.14
	Guangdong	374	57.49	3.48
	Guangxi	393	22.90	0.76

(0.75% of samples), followed by isocarbophos (0.51%), isoprothiolane (0.47%), fipronil (0.26%), and imidacloprid (0.22%). The highest concentrations were found for chlorpyrifos (4.22 $mg\,kg^{-1}$), thiamethoxam (3.71 $mg\,kg^{-1}$), isoprothiolane (1.89 $mg\,kg^{-1}$), and carbendazim (1.59 $mg\,kg^{-1}$). Methamidophos, fipronil, and isocarbophos were banned from agricultural use in China in 2007, 2009, and 2020, respectively. However, their residues were still detected in rice samples in this study, suggesting that it is necessary to strengthen the supervision and management of banned and restricted pesticides in rice.

3.4. The Cooccurrence of Multiple Pesticide Residues. Multiple pesticide residues were present in brown rice samples, as shown in Figure 3. The 17.7% (1102) of rice samples contained more than two pesticide residues in 6,229 rice samples, of which 10.10% (629) of the samples contained two pesticide residues, 3.89% (242) contained three pesticide residues, 2.28% (142) contained four pesticide residues, and 1.43% (89) contained five or more pesticide residues. One brown rice sample was contaminated by 10 pesticide residues, indicating the cooccurrence of multiple pesticide residues in rice grain.

3.5. Risk Ranking. The 25 pesticides were classified into three groups according to the residual risk score listed in Figure 4. The 32.0% (8) of the pesticides had a high risk with a score >20, 20.0% (5) had a medium risk of 15–20, and 48.0% (12) had a low risk with <15. Carbofuran, methamidophos, and isocarbophos had the highest risk scores of 25.09, 25.01, and 25.00, respectively, due to their high toxicity to mammals by inhibiting AChE activities. Additionally, chlorpyrifos, dimethoate, isoprocarb, triazophos, and fipronil had a relatively higher risk score of 20.22, 20.18, 20.11, 20.02, and 20.00, respectively, due to their moderate toxicities. Except for the banned and restricted pesticides of methamidophos, fipronil, and isocarbophos, most of the pesticides with high residual risk scores can be legally applied on rice, indicating that it is crucial to decrease the use of highly and moderately toxic pesticides on rice to minimize the health risk of pesticide residues in rice grain.

3.6. Dietary Exposure and Risk Assessment

3.6.1. Chronic and Acute Dietary Exposure Risk. The chronic dietary exposure risk for each pesticide was calculated based on STMR residuals and the mean daily rice intake for Chinese residents. The HQ_c for 25 pesticides ranged from 4.54×10^{-6} to 4.21×10^{-2} for children and adolescents and 2.29×10^{-6} to 2.12×10^{-2} for adults and the elderly, of which all HQ_c values were much smaller than 1 (Table 5). Among all pesticides, isocarbophos had the highest HQ_c values (4.21×10^{-2} for children and adolescents, 2.12×10^{-2} for adults and the elderly), followed by dimethoate (4.17×10^{-2} and 2.10×10^{-2}) and carbofuran (4.16×10^{-2} and 2.10×10^{-2}).

Table 4: The frequencies and concentration ranges of detected pesticide residues in brown rice from the three main rice-producing regions in China during 2016–2020.

Pesticides	No. of pesticides detected (%)	No. of pesticides over MRLs (%)	Detection concentration (mg/kg)		
			Min-Max	Mean[a]	Median[a]
Methamidophos	0.53	0.00	<LOD-0.1509	0.0005	0.0004
Pymetrozine	0.11	0.00	<LOD-0.0359	0.0085	0.0085
Nitenpyram	0.22	0.00	<LOD-0.0090	0.0020	0.0020
Carbendazim	8.32	0.00	<LOD-1.5887	0.0009	0.0001
Thiamethoxam	0.13	0.02	<LOD-3.7100	0.0256	0.0250
Clothianidin	1.43	0.06	<LOD-0.7101	0.0031	0.0026
Imidacloprid	1.72	0.22	<LOD-0.2104	0.0034	0.0030
Dimethoate	0.29	0.00	<LOD-0.0450	0.0101	0.0100
Acetamiprid	0.06	0.00	<LOD-0.4762	0.1002	0.1000
Carbofuran	0.06	0.00	<LOD-0.0439	0.0050	0.0050
Isoprocarb	0.66	0.00	<LOD-0.1679	0.0052	0.0050
Chlorantraniliprole	2.63	0.00	<LOD-0.1100	0.0029	0.0025
Isocarbophos	1.14	0.51	<LOD-0.6244	0.0160	0.0150
Fenobucarb	0.08	0.00	<LOD-0.3215	0.0076	0.0075
Azoxystrobin	3.74	0.00	<LOD-0.0730	0.0004	0.0001
Triadimefon	0.80	0.00	<LOD-0.1708	0.0006	0.0005
Tebuconazole	7.08	0.00	<LOD-0.3400	0.0024	0.0005
Triazophos	4.61	0.75	<LOD-0.7305	0.0019	0.0002
Isoprothiolane	13.57	0.47	<LOD-1.8887	0.0197	0.0002
Fipronil	1.54	0.26	<LOD-0.0750	0.0006	0.0004
Propiconazole	5.94	0.05	<LOD-1.0130	0.0019	0.0005
Prochloraz	0.29	0.00	<LOD-0.0392	0.0003	0.0003
Difenoconazole	0.77	0.00	<LOD-0.3221	0.0053	0.0050
Chlorpyrifos	4.59	0.03	<LOD-4.2200	0.0065	0.0040
Buprofezin	2.55	0.08	<LOD-0.5100	0.0040	0.0025

[a]The concentration lower than LOD was treated as one-half of LOD when calculating the mean and median values.

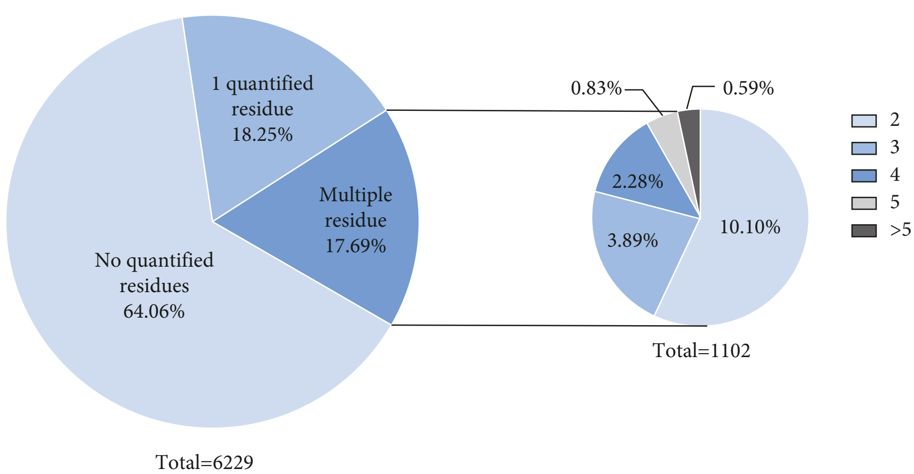

Figure 3: Proportions of pesticide residues in a single brown rice sample.

The acute dietary exposure risks for isocarbophos, fenobucarb, isoprocarb, nitenpyram, chlorantraniliprole, isoprothiolane, and azoxystrobin are not shown because their ARfD values were not available or unnecessary in the JMRP database. The HQ_a values for the other 18 pesticides ranged from 5.82×10^{-5} to 0.11 for children and adolescents and 2.95×10^{-5} to 5.58×10^{-2} for adults and the elderly, which were much smaller than 1 (Table 5). Carbofuran had the highest HQ_a values (0.11 for children and adolescents, 5.58×10^{-2} for adults and the elderly), followed by acetamiprid (2.20×10^{-2} and 1.12×10^{-2}) and dimethoate (1.12×10^{-2} and 5.66×10^{-3}). These results suggest that the current chronic and acute dietary exposure risks to an individual pesticide from rice consumption are acceptable for the Chinese population.

3.6.2. Cumulative Dietary Exposure Risk. The cumulative risks of exposure to OPs, NEOs, and TFs were performed based on the RPF approach. As shown in Table 6, for the

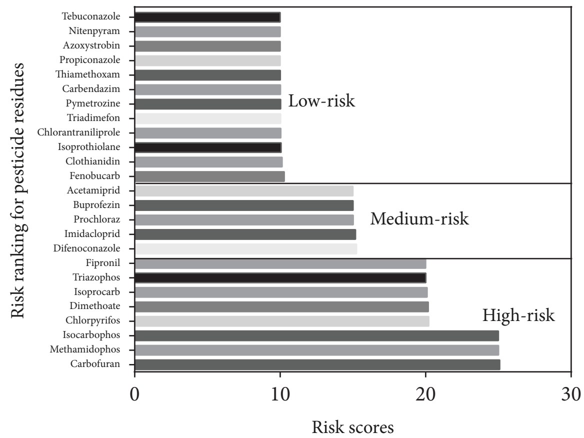

Figure 4: Risk ranking for pesticide residues in brown rice sample. High risk with a score >20, medium risk with a score of 15–20, and low risk with a score <15.

Table 5: Chronic and acute dietary exposure risk assessments of pesticide residues (mg/kg bw/day) in brown rice.

Pesticides	Chronic risk					Acute risk				
	ADI[a]	Children and adolescents		Adults and the elderly		ARfD[b]	Children and adolescents		Adults and the elderly	
		EDI	HQ_c	EDI	HQ_c		EDI	HQ_a	EDI	HQ_a
Methamidophos	0.004	3.37E-06	8.41E-04	1.69E-06	4.24E-04	0.01	9.79E-06	9.79E-04	4.96E-06	4.96E-04
Pymetrozine	0.03	7.08E-05	2.36E-03	3.56E-05	1.19E-03	0.1	1.87E-04	1.87E-03	9.48E-05	9.48E-04
Nitenpyram	0.53	1.67E-05	3.14E-05	8.39E-06	1.58E-05	—	4.45E-05	—	2.26E-05	—
Carbendazim	0.03	4.94E-07	1.65E-05	2.49E-07	8.29E-06	0.1	5.97E-06	5.97E-05	3.03E-06	3.03E-05
Thiamethoxam	0.08	2.08E-04	2.60E-03	1.05E-04	1.31E-03	1	5.53E-04	5.53E-04	2.80E-04	2.80E-04
Clothianidin	0.1	2.12E-05	2.12E-04	1.07E-05	1.07E-04	0.6	6.70E-05	1.12E-04	3.39E-05	5.66E-05
Imidacloprid	0.06	2.55E-05	4.25E-04	1.28E-05	2.14E-04	0.4	8.11E-05	2.03E-04	4.11E-05	1.03E-04
Dimethoate	0.002	8.34E-05	4.17E-02	4.20E-05	2.10E-02	0.02	2.23E-04	1.12E-02	1.13E-04	5.66E-03
Acetamiprid	0.07	8.32E-04	1.19E-02	4.19E-04	5.99E-03	0.1	2.20E-03	2.20E-02	1.12E-03	1.12E-02
Carbofuran	0.001	4.16E-05	4.16E-02	2.10E-05	2.10E-02	0.001	1.10E-04	0.11	5.58E-05	5.58E-02
Isoprocarb	0.002	4.18E-05	2.09E-02	2.11E-05	1.05E-02	—	1.15E-04	—	5.83E-05	—
Chlorantraniliprole	2	2.14E-05	1.07E-05	1.08E-05	5.39E-06	Unnecessary	7.25E-05	—	3.67E-05	—
Isocarbophos	0.003	1.26E-04	4.21E-02	6.35E-05	2.12E-02	—	3.66E-04	—	1.86E-04	—
Fenobucarb	0.06	6.25E-05	1.04E-03	3.15E-05	5.24E-04	—	1.66E-04	—	8.41E-05	—
Azoxystrobin	0.2	9.08E-07	4.54E-06	4.58E-07	2.29E-06	Unnecessary	5.24E-06	—	2.66E-06	—
Triadimefon	0.03	4.21E-06	1.40E-04	2.12E-06	7.07E-05	0.08	1.23E-05	1.54E-04	6.26E-06	7.82E-05
Tebuconazole	0.03	4.87E-06	1.62E-04	2.45E-06	8.17E-05	0.3	5.18E-05	1.73E-04	2.62E-05	8.75E-05
Triazophos	0.001	1.40E-06	1.40E-03	7.05E-07	7.05E-04	0.001	1.04E-05	1.04E-02	5.25E-06	5.25E-03
Isoprothiolane	0.1	1.90E-06	1.90E-05	9.57E-07	9.57E-06	Unnecessary	2.15E-04	—	1.09E-04	—
Fipronil	0.0002	3.42E-06	1.71E-02	1.72E-06	8.61E-03	0.003	1.15E-05	3.83E-03	5.83E-06	1.94E-03
Propiconazole	0.07	4.28E-06	6.12E-05	2.16E-06	3.08E-05	0.3	3.72E-05	1.24E-04	1.88E-05	6.28E-05
Prochloraz	0.01	2.09E-06	2.09E-04	1.05E-06	1.05E-04	0.1	5.82E-06	5.82E-05	2.95E-06	2.95E-05
Difenoconazole	0.01	4.19E-05	4.19E-03	2.11E-05	2.11E-03	0.3	1.18E-04	3.95E-04	6.00E-05	2.00E-04
Chlorpyrifos	0.01	3.51E-05	3.51E-03	1.77E-05	1.77E-03	0.1	1.47E-04	1.47E-03	7.46E-05	7.46E-04
Buprofezin	0.009	2.16E-05	2.40E-03	1.09E-05	1.21E-03	0.5	8.09E-05	1.62E-04	4.10E-05	8.20E-05

[a]Acceptable daily intake (mg/kg bw/day) was obtained by GB 2763-2019, China. [b] Acute reference dose (mg/kg bw/day) was obtained from the JMPR database (https://apps.who.int/pesticide-residues-jmpr-database/).[c] No ARfD values in the JMPR database.

chronic cumulative risk of exposure, the HI_c values for OPs, NEOs, and TFs were 4.37×10^{-3}, 1.42×10^{-2}, and 3.69×10^{-3} for children and adolescents, respectively, and correspondingly 2.20×10^{-3}, 7.14×10^{-3}, and 1.86×10^{-3} for adults and the elderly, which were all smaller than 1 (Table 6). For acute cumulative risk of exposure, the HI_a values for OPs, NEOs, and TFs were 3.36×10^{-2}, 2.40×10^{-2}, and 1.47×10^{-3} for children and adolescents, respectively, and correspondingly 1.70×10^{-2}, 1.22×10^{-2}, and 7.43×10^{-4} for adults and the elderly, also smaller than 1 (Table 6). The results suggest that the cumulative risks of chronic and acute dietary exposure to OPs, NEOs, and TFs from rice consumption are not of health concern.

Table 6: Cumulative risk assessments of chronic and acute dietary exposure (mg/kg bw/day) to pesticide groups in brown rice.

Groups	Pesticides	NOAEL[a]	RPF	Chronic effect: Children and adolescents		Chronic effect: Adults and the elderly		NOAEL[b]	RPF	Acute effect: Children and adolescents		Acute effect: Adults and the elderly	
				EDI × RPF	HI_c	EDI × RPF	HI_c			EDI × RPF	HI_a	EDI × RPF	HI_a
OPs	Methamidophosc (IC)[c]	0.1	1.00	3.37E-06	3.69E-03	1.69E-06	1.86E-03	0.3	1.00	9.79E-06	3.36E-02	4.96E-06	1.70E-02
	Triazophos	0.15	0.67	9.34E-07		4.70E-07		0.0125	24.00	2.48E-04		1.26E-04	
	Chlorpyrifos	1	0.10	3.51E-06		1.77E-06		1	0.30	4.42E-05		2.24E-05	
	Dimethoate	1.2	0.08	6.95E-06		3.50E-06		2	0.15	3.35E-05		1.70E-05	
NEOs	Imidacloprid (IC)	5.7	1.00	2.55E-05	1.42E-02	1.28E-05	7.14E-03	42	1.00	8.11E-05	2.40E-02	4.11E-05	1.22E-02
	Thiamethoxam	8.23	0.69	1.44E-04		7.26E-05		100	0.42	2.32E-04		1.18E-04	
	Acetamiprid	7.1	0.80	6.68E-04		3.37E-04		10	4.20	9.24E-03		4.68E-03	
	Clothianidin	9.7	0.59	1.25E-05		6.28E-06		60	0.70	4.69E-05		2.38E-05	
TFs	Difenoconazole (IC)	1	1.00	4.19E-05	4.37E-03	2.11E-05	2.20E-03	100	1.00	1.18E-04	1.47E-03	6.00E-05	7.43E-04
	Propiconazole	3.6	0.28	1.19E-06		5.99E-07		30	3.33	1.24E-04		6.28E-05	
	Tebuconazole	16	0.06	3.04E-07		1.53E-07		30	3.33	1.73E-04		8.75E-05	
	Triadimefon	16.4	0.06	2.57E-07		1.29E-07		50	2.00	2.47E-05		1.25E-05	

[a]No observed adverse effect level (mg/kg bw/day) of chronic effect, obtained from the JMPR and EFSA (2009).[b]No observed adverse effect level (mg/kg bw/day) of acute effect obtained from the JMPR and EFSA (2009).[c]Index compound.

4. Discussion

Pesticides are widely used to control diseases and pests and improve rice production in China. However, excessive pesticide application has caused significant risks to the paddy environment and human health. To alleviate this problem, in 2015, China's Ministry of Agricultural and Rural Affairs introduced two actions to achieve zero growth in chemical fertilizer and pesticide use by 2020, also named the "Dual Reductions of Chemical Fertilizer and Pesticides" program [42]. With the implementation of the program, the total amount of pesticides used per year decreased from 1.78 million tons in 2015 to 1.39 million tons in 2020. The utilization rate of pesticides increased from 36.6% in 2015 to 40.6% in 2020, according to the data published by the National Bureau of Statistics of China, resulting in the decreased contamination level of pesticide residues in rice grain in China from 2016 to 2020 in the present study (Table 2). Besides China, rice is the main stable food in many countries, and pesticide residue in rice has attracted worldwide attention. In Brazil and Saudi Arabia, about 48% of rice samples contained one or multiple pesticides [23, 43]. The detection frequencies of organochlorine in rice samples from Thailand were over 58% [31]. Thus, the contamination level of pesticide residues in rice grain in China is relatively lower than that in other countries. Moreover, there were significant regional variations in pesticide residue levels in rice grain in China. The Yangtze River basin had the highest detection rate and over MRL rate of pesticide residues compared with other regions (Table 3). It is well known that the Yangtze River basin is the "land of fish and rice," accounting for nearly 65.7% of the total national rice planting area in China. High temperature and abundant rainfall during the rice growing season in this region provide conditions for the widespread occurrence of diseases and pests, such as rice blast, sheath blight, rice false smut disease, rice planthopper, and rice leaf roller [44], resulting in an excessive application of pesticides and subsequent pesticide residue contamination in rice grain. Therefore, it is crucial to improve plant disease and pest management, including the use of resistant varieties, parasitism, or predation on pests or parasites, and natural pesticides from botanical and mineral sources [45], which could fundamentally reduce the application of chemical pesticides.

Among all pesticides analyzed in this study, isoprothiolane and carbendazim were the most detected, with detection rates of 13.57% and 8.32%, respectively (Table 4). Isoprothiolane is a highly effective systemic fungicide that controls the rice blast disease, one of the most widespread and destructive fungal diseases in China. It can be absorbed by rice roots and leaves and inhibits pathogen infection [46]. Carbendazim is a broad-spectrum fungicide that inhibits the synthesis of β-tubulin and has been extensively applied in agricultural, horticultural, and forestry crops [47]. Rice is affected by various fungal diseases in China, including rice blast (*Magnaporthe grisea*), sheath blight (*Rhizoctonia solani*), and false smut disease (*Ustilaginoidea virens*), resulting in significantly decreased grain yield [44]. Correspondingly, the extensive use of isoprothiolane and carbendazim for controlling the above fungal diseases might lead to higher residue levels in rice grain. Pesticide residues exceeding the MRLs were found most often in triazophos (0.75%), isocarbophos (0.51%), isoprothiolane (0.47%), fipronil (0.26%), and imidacloprid (0.22%), and the over MRL rates were all very low (Table 4). Triazophos is an important OP insecticide for controlling bollworms on paddy fields in the Yangtze River basin. It is moderately toxic to mammals but highly toxic to aquatic organisms [48]. The use of triazophos on vegetables has been banned in China since 2016, but it is still widely used on rice and cotton. The residues of triazophos exceeding the MRLs in this study might be due to its indiscriminate use, relatively high stability, and long half-life [48]. The banned and restricted pesticide residues of methamidophos, fipronil, and isocarbophos were detected in rice samples, which have a relatively higher risk score than other pesticides (Table 4, Figure 4). Therefore, it is necessary to strengthen the supervision and management of these pesticides. In addition, the coexistence of multiple pesticide residues was detected in rice samples, and 17.7% (1102) of rice samples contained two or more pesticide residues (Figure 3). Similar results have been reported in other crops. The 23.7% (40) of tea samples contained two or more OPs [49]. Cui et al. [28] reported that more than 30% of rice, grape, and mandarin samples contained more than three TF residues. Thus, the coexistence of multiple pesticide residues in crops is very common in China. Extensive studies have demonstrated that the coexistence of multiple residues in the same sample could cause joint toxicities to the environment and human health [50, 51]. Regulation (EC) (no. 396/2005) has proposed that the cumulative and synergistic effects of multiple pesticides should be considered when establishing MRLs since 2008. However, current food safety standards from China and other countries only concern individual pesticides, which may underestimate the health risk of pesticides in foods. Thus, more work should be done to establish MRLs for the cooccurrence of multiple pesticide residues.

The values for both HQ_c and HQ_a for the 25 pesticides were much smaller than 1 (Table 5), and HI_c and HI_a for OP, NEO, and TF groups were also much smaller than 1 (Table 6), suggesting that the cumulative chronic and acute risks of dietary exposure to OPs, NEOs, and TFs from rice consumption are acceptable for the Chinese population, which is consistent with the current studies. Jardim et al. [23] reported that the cumulative intakes at the 99.9th percentile for CBs and OPs due to rice consumption ranged from 7.55×10^{-3} to $1.39 \times 10^{-1}\,\mu$g/g bw/day for the Brazilian population, which did not exceed the ARfD (1 μg/g bw/day) and the risks from the exposure were not considered of health concern. Similarly, Almutairi et al. [43] found that the HI value for pesticides through rice consumption was 6.8×10^{-3}, which was much less than 1, implying no obvious noncarcinogenic risk of cumulative exposure to pesticides in rice for the Saudi population. Cui et al. [27, 28] also showed that the HI_c and HI_a values for NEOs and TFs *via* rice were in the range of 5.00×10^{-4} and 2.33×10^{-3}, suggesting that the cumulative chronic and acute exposure to NEOs and TFs from rice are far below levels that might pose a health risk for the Chinese population. Moreover, the relatively higher risk of dietary exposure to pesticide residues for children and adolescents should be paid more attention to because of their higher rice intake per kg body weight (Tables 5 and 6). Although 25 pesticides in 6,229 rice samples from 17 provinces in China were analyzed and the cumulative chronic and acute risks of dietary exposure to pesticides in brown rice were discussed, there were some limitations in our study. First, the rice consumption and body weight information were obtained from the WHO database in 2002, which cannot reflect the actual levels for the current Chinese population. Second, the number of pesticides in each pesticide group for the cumulative risk assessment was relatively low owing to the NOAELs of some pesticides not being available in databases. Therefore, the health risk of cumulative dietary exposure to pesticides was partly underestimated. Third, the food processing factors for rice intake were not considered in this study due to the relatively simple processing of rice.

5. Conclusions

In summary, the contamination level of pesticide residues in rice grains in China decreased during 2016–2020. The Yangtze River basin had a higher detection rate and over MRL rate compared with the other regions. Isoprothiolane and carbendazim were the most frequently detected pesticides, with detection rates of 13.57% and 8.32%, respectively, and pesticide residues exceeding the MRLs were found most often in triazophos and isocarbophos, with over MRL rates smaller than 1%. Carbofuran, methamidophos, and isocarbophos had the highest residual risk scores of 25.09, 25.01, and 25.00, respectively. The 17.7% (1,102) of rice samples contained two or more pesticide residues. The cumulative chronic and acute dietary exposures to OPs, NEOs, and TFs from rice consumption were not considered of health concern. The cumulative risks of dietary exposure to pesticides for children and adolescents were higher than those for adults and the elderly due to their higher rice intake per kg body weight. The study provides national-scale information on the contamination levels and health risks of pesticide residues in rice, which can help develop continuous monitoring programs for pesticide residue contamination in rice in China.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Figure S1: the chromatograms of 25 pesticides in a standard mixture at 0.1 mg L^{-1}. Table S1: the optimized MRM parameters of 25 pesticides analyzed in this study. Table S2: ranking criteria of pesticide risk in brown rice. Table S3: the daily rice intake per kilogram of body weight (g/kg.bw/day) for Chinese residents. (*Supplementary Materials*)

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