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Prioritization of pesticides in crops with a semi-quantitative risk ranking method for Taiwan postmarket monitoring program



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ABSTRACT

A risk-based prioritization of chemical hazards in monitoring programs allows regulatory agencies to focus on the most potentially concerned items involving human health risk. In this study, a risk-based matrix, with a scoring method using multiple factors for severity and probability of exposure, was employed to identify the pesticides presented in crops that may pose the greatest risk to human health. Both the probability of exposure and the severity were assessed for 91 pesticides detected in a Taiwanese postmarketing monitoring program. Probability of exposure was evaluated based on the probability of consumption and evidence of pesticide residues in crops. Severity was assessed based on the nature of the hazard (i.e., the description of toxic effects), and the acceptable daily intake (ADI) reported by available toxicological reports. This study showed that the nature of the hazard and probability of consumption had the strongest contribution to risk score. Dithiocarbamates, endosulfan, and carbofuran were identified as the pesticides with the highest concern for human health risks in Taiwan. These pesticides should be monitored more frequently than others in crops during the postmarketing monitoring program. However, some uncertainties shall be noted or improved when this methodology is applied for risk prioritization in the future.

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1. Introduction

Control of pesticide hazards is important because pesticides are suspected to be associated with a broad spectrum of adverse health effects [1,2]. Monitoring of pesticides has been conducted

in food safety marketing programs to ensure compliance with the maximum permissible residue levels (MRLs) of pesticides in food [3]. However, a wide range of pesticides may be present in crops, and commonly, there are insufficient resources to manage all the pesticides at any given time. Therefore, a monitoring program should use the risk-based approach,

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allowing efficient resource allocation for specifically targeting the pesticides that pose the greatest human health risk. Applying a risk-based prioritization method was demonstrated to not only increase the detection probability, but also decreased the inspection costs [4]. For cost-effective use of resources, the risk-based prioritization approach is necessary for prioritizing pesticides in food safety monitoring programs.

The risk-based prioritization strategy has been used for a long time to rank chemicals that pose a health risk [5]. Hazard ranking of environmental chemicals is usually applied to incomplete databases and dependent on the detection possibilities rather than on the concentrations of contaminants [6–8]. Some approaches involve the use of toxicity information to assess the hazard of chemicals without using exposure information [9,10]. Recently, various risk-based ranking approaches have been developed and are available for use in food safety monitoring programs. In the European Union (EU), the European Food Safety Authority (EFSA) published a series of opinions regarding meat inspection to rank the risk of both biological hazards and chemical hazards based on various qualitative methods, including risk ratios and decision trees [11–16]. Moreover, a semiquantitative risk-scoring system was used to prioritize substances as per their residues. In the United States, the food safety inspection service has developed scheduled sampling plans for domestic and imported veterinary drugs in their national residue program [17]. The Belgian Federal Agency for the Safety of the Food Chain scores chemical hazards based on their toxicities, prevalence, and exposure [18]. The most comprehensive risk-ranking matrix was developed by the UK Veterinary Residues Committee (VRC) [19] for prioritizing the testing of veterinary medicine residues. These risk-ranking approaches use a risk matrix framework that combines probability (e.g., likelihood of exposure) and severity (severity of the effect) to semiquantitatively estimate the risk posed by substances. The nature of a substance, usage of the substance, substance's residue occurrence, and dietary exposure to the substance are incorporated and scored on a scale from high to low. This ranking system is limited to veterinary drug residues; however, it involves complete consideration of the nature of the hazard, including acute and chronic toxicities; acceptable daily intakes (ADIs) of pesticides; consumption of pesticides; and evidence of detectable residues.

More than 360 pesticides can be detected, but limited resources are available to monitoring programs; therefore, a risk-based ranking method is needed for favorable allocation of resources and identification of the substances that pose health concerns. The aim of the present study was to derive a risk-ranking method based on the VRC's scoring system [19] that prioritizes the risks of pesticides in food and recommends pesticides for inspection in the monitoring program in Taiwan. We employed this method of prioritizing pesticide detection to crops in the Taiwanese postmarketing food safety monitoring program.

2. Materials and methods

2.1. Study framework

A general risk-ranking method was derived from the approach used in the UK [19]; the study framework is illustrated in Fig. 1.

Risk is defined as a function of severity and probability of exposure. The probability of exposure in this case was evaluated from the possible exposure to a pesticide as well as the evidence of the pesticide's detection in the selected crops (Fig. 1A). The severity was estimated using the description of the toxic effects (i.e., the nature of the hazard) and toxicological reference values (i.e., the ADI) (Fig. 1B). The combination of these two elements provides a risk-based prioritized ranking of pesticides (Fig. 1C). The various items are scored on a scale from high to low (Table 1). Based on the scores attributed to the two aforementioned factors, the risk of a pesticide can be ranked from high to low.

2.2. Study data

In this study, the pesticides in crops were analyzed based on the results of the 2014 Taiwan post-marketing monitoring program. The Taiwan Food and Drug Administration (TFDA) and regional Health Bureaus regularly collected more than 2500 samples from agricultural food products in retail markets, traditional markets, supermarkets, restaurants, and wholesale markets. The selected crops were classified into the following 13 different groups: rice, leafy vegetables, brassica vegetables, root and tuber vegetables, fruiting vegetables, small berries, stone fruits, tea, pome fruits, melon vegetables, legume vegetables, citrus fruits, and spice plants. All the samples were analyzed for 103 pesticide residues by the Central Region Laboratory of the Taiwan Food and Drug Administration (TFDA). However, only data of non-compliant pesticides were available and included in this study.

2.3. Risk-ranking method for pesticides

The overall risk-ranking method ranked pesticides using severity $\times$ probability of exposure. The severity of a hazard was estimated based on the nature of the hazard (factor A) as well as the ADI of pesticides (factor B). The probability of exposure was estimated using two independent factors: the probability of consumption of crops containing pesticides (factor C) and the evidence of pesticide residues in crops (factor D). The equation is as follows:

$$\text{Risk score} = (A + B) \times C \times D \quad (1)$$

2.3.1. Nature of the hazard

Toxicological data were collected from the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), EFSA, and the United States Environmental Protection Agency (US EPA) reports. First, we assessed the evidence of mutagenicity, sensitization, and carcinogenicity in the reports. The toxicological endpoints of No Observed Adverse Effect Level (NOAEL) for determining the ADI were collected for scoring. If a pesticide also had NOAELs for other toxicological endpoints, with levels less than 10-fold of the ADI, these toxicological endpoints were also included in the scoring. The toxicological endpoints were classified as reversible pharmacological effects; reversible organ toxicity; sensitization; possible human carcinogenic effects, irreversible organ toxicity, fetotoxicity, embryotoxicity, or immunotoxicological effects; probable

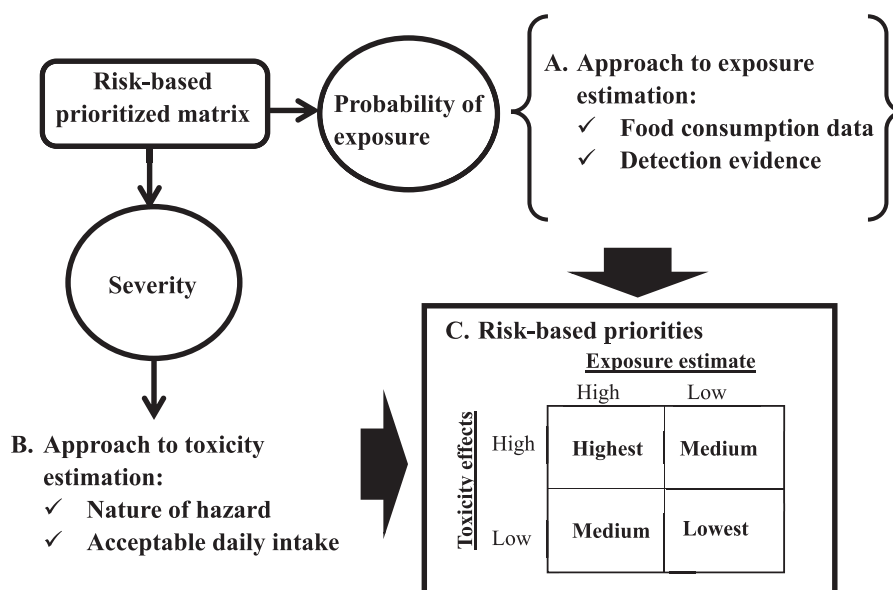


Fig. 1 – Framework of the risk-ranking matrix study.

human carcinogenic effects, prenatal neurotoxic effects, irreversible reproductive or developmental effects, or mutagenicity effects and neurotoxic effects; reproductive and developmental toxicity; mutagenesis; and human carcinogenic effects (see the [supplementary information for details](#)). Carcinogenicity was determined using the criteria of the US EPA [20]. Based on the scoring systems, the nature of the hazard (factors A) was ranked on a scale from 1 to 6 (low–high) to represent the severity of toxicity (Table 1).

2.3.2. ADI

We obtained the ADIs of the 103 detected pesticides from the JMPR or other reports (e.g., EFSA). Of these pesticides, only 91

had an established ADI, the toxicological reference value necessary for characterizing a pesticide's chronic risk. ADIs were not proposed in the JMPR or EFSA reports for the other 12 pesticides because of inadequate or absent toxicological data. The score ranges for factor B was established using the quartile of the log-transformed ADI and was 1–4 (Table 1).

2.3.3. Probability of consumption of crops containing pesticides

The probability of consumption of crops containing pesticides (factor C) was scored based on consumption data from the Taiwan Food Consumption Database as well as from the probability of detecting pesticide residues in crops. The

Table 1 – Scores attributed to the various risk factors of pesticides.

Score	(A): Nature of the hazard ^a	(B): ADI (mg/kg-d)	(C): Probability of consumption of crops containing pesticides (g/d) ^b	(D): Evidence of pesticide residues in crops
1	Reversible adverse pharmacological effects (e.g., increased blood pressure or heart rate).	>10	<0.24	Pesticide residues below the MRL
2	Reversible organ toxicity (e.g. kidney or liver damage).	>0.1–10	0.24 ~ <0.91	Pesticide residues above the MRL
3	Evidence of allergic reactions in animals.	>0.001–0.1	0.91 ~ <2.31	Pesticide residues violation
4	Possible human carcinogen ^c . Irreversible organ toxicity. Fetotoxicity/embryotoxicity.	≤0.001	≥2.31	Banned pesticides
5	Immunotoxicological effects Probable human carcinogen ^c . Irreversible neurotoxic effects. Prenatal reproductive/development effects. Mutagenicity effects.			
6	Evidence of carcinogenicity in humans. Carcinogenic by mechanisms relevant to human ^c .			

^a The nature of the hazard was categorized based on toxicological data from JMPR reports.

^b The food consumption data were grouped by quartiles: <25%, 25%–<50%, 50%–<75%, ≥75%.

^c Carcinogens were classified based on the USEPA guidelines (USEPA, 2005).

consumption database contains data gathered on food consumption from 3819 individuals of the general population (age ranging from <3 to 65 years) from the Nutrition and Health Survey in Taiwan (NAHSIT) 2005–2012. Based on these data, the median consumption (g/d) on consumption days and the overall consumption were recorded per food group. These data allowed us to estimate pesticide consumption due to crops in the diet. The equation for calculating the consumption is

$$\text{Consumption of pesticides} = \sum_{ij} C_i \times E_{ij} \quad (2)$$

where C_i is the consumption of crops i and E_{ij} is the probability of detecting pesticide residues j in crops i . The score range for factor C was established by quartiles and was 1–4.

2.3.4. Evidence of pesticide residues in crops

The evidence that the pesticide residues detected in crops (factor D) was analyzed based on the results of the Taiwanese postmarket surveillance of foods in 2014. The TFDA and local Health Bureaus regularly collected samples belonging to various categories from a total of 2340 crops. The samples were randomly collected from 13 categories of crops, in accordance with the food items listed in the NAHSIT. Based on the criteria in Table 1, the evidence of detection could be analyzed and quantified from a score of 1–4. Pesticide residues violation and banned pesticides were scored 3 and 4, respectively. Pesticide residues violation is defined as the application of pesticide to the wrong crops. A banned pesticide is defined as a pesticide for which all registered uses have been prohibited by final government action. Because only data of non-compliant pesticides were available and included in this study, pesticides residues lower than MRL (factor D = 1) were not included in this study.

2.4. Sensitivity analyses

Sensitivity analyses were performed by estimating the contribution of each factor to the variance in the risk score. The contribution of each factor was determined by squaring the Spearman rank correlation coefficient and then normalizing to 100% (Eq (3)). The sensitivity analyses were performed using Oracle Crystal Ball software (version 11.1.1).

$$P_i = \frac{\omega_i^2}{\sum_i \omega_i^2} \times 100\% \quad (3)$$

where ω_i is the Spearman rank correlation coefficient between the input parameter i and the outcome, and P_i is the contribution to the risk score variance of the indicator i .

3. Results

A total of 91 pesticides were ranked in this study. Factors A and B were the indicators of toxicity estimation. Factor A was scored according to the animal studies summarized in JMPR or EFSA reports. Among the analyzed pesticides, 40 pesticides had the highest potential hazard with irreversible neurotoxic or reproductive effects (score 5); 28 pesticides were potential

animal carcinogens or had the potential to cause irreversible organ toxicities (score 4), and 6 pesticides caused allergic reactions (score 3) in animal studies. The other detected pesticides had adverse but reversible pharmacological effects (5 pesticides) (score 1) or reversible organ toxicity (12 pesticides) (score 2). The toxicities were assigned scores ranging from 1 to 6, as described in Table 1.

A total of 103 pesticides were scored based on their ADI to comprise factor B. However, 11 pesticides had no ADI in the JMPR and EFSA summary reports because inadequate toxicity data were available; thus, these 11 pesticides were neither scored nor included in the ranking results. Another exception was omethoate, for which the ADI was withdrawn in 1996 [21] (the previous ADI was 0.0003 mg/kg-d) because the primary manufacturer discontinued its production. Thus, we analyzed the 91 pesticides in this study after excluding the 12 pesticides without an ADI. A four-point coding system was applied to the ADI values. Overall, 10 pesticides with ADI >0.1–10 mg/kg-d were assigned a score of 2; 76 pesticides with moderate ADI (>0.001–0.1 mg/kg-d) were assigned a score of 3; and the 5 pesticides with the lowest ADI (≤ 0.001 mg/kg-d) were assigned a score of 4.

Factor C (probability of consumption) was scored based on the consumption data for Taiwan to indicate the possible ingestion of pesticide residues through overall consumption of the products available. Based on consumption that ranged from 0.24 to 2.31 g/d, factor C has been attributed a score ranging from 1 to 4 by categorizing this range into quartiles. Overall, 31 pesticides with high consumption were attributed a score of 4. The pesticides with the highest consumption were dimethomorph, difenoconazole, endosulfan, and propargite.

Factor D (evidence of pesticide residues in crops) was scored as described in Table 1. Factor D was categorized based on the detection of pesticides at concentrations, lower or higher than the MRL as well as if a pesticide use is violation or banned. However, the samples of compliant pesticides (factor D = 1) were not included in our present study. Among all the detected pesticides, 7 were present in concentrations higher than the MRL (score 2), and 82 pesticide-use violations were detected (score 3) (i.e., violate used in specific crop items). Only 2 banned pesticides (scored 4), dithiocarbamates and endosulfan, were detected in the postmarket samples. Although dithiocarbamates are a broad pesticides class, part of compounds has been banned in Taiwan such as amobam, cufaneb, zineb, and ziram. Thus, we refer dithiocarbamates to the banned pesticides.

Overall, the pesticide ranking score ranged from 20 to 128 (Fig. 2); 15 pesticides had high risk scores (Table 2), which was 16% of the 91 total pesticides. Dithiocarbamates, endosulfan, and carbofuran were assigned scores of 128, 112, and 108, respectively, making them the pesticides of highest concern to human health in Taiwan. These results provide recommendations for establishing priorities for pesticide management in the future.

Using the results of the sensitivity analyses, the contribution of each factor to the variance in the risk-ranking score was calculated (Fig. 3). The probability of consumption (factor C) and nature of the hazard (factor A) were the most important parameters that contributed 44.3% and 39.7%, respectively. ADI (factor B) contributed to more than 10% of the variance.

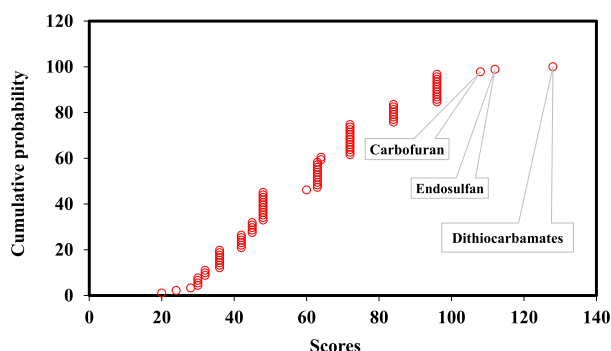


Fig. 2 – Risk scores of all pesticides. Risk scores were calculated using Eq. (2) based on the data of 91 pesticides. The X-axis indicates the risk score, and the Y-axis represents the cumulative probability of ranking numbers.

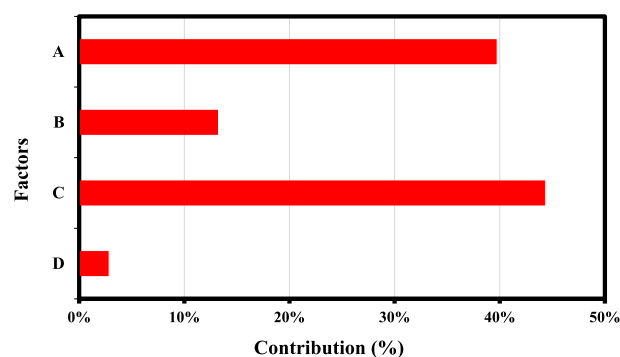


Fig. 3 – Sensitivity analyses. Contribution to the variance of risk scores was calculated using Eq. (3). The X-axis indicates the risk factors in the risk-based ranking matrix, and the Y-axis represents the percentages that contributed to the variance in risk scores.

The results showed that the nature of the hazard (factor A) had a strong contribution to the ranking score in our data.

The classification of factor A was based on the description of toxic effects in the JMPR toxicological reference, which varied by the target organ, and chronic toxicity in animal studies. A high percentage of pesticides (45%) was classified into the category of possible human carcinogens and those causing irreversible organ toxicity, fetotoxicity, embryotoxicity, or immunotoxicological effects; 19% were in the category of those responsible for reverse organ toxicity; 16% were in the category of probable human carcinogens or those that cause irreversible neurotoxic, adverse reproductive, or mutagenicity

effects; 9% were irritants, and 8% were those responsible for reversible adverse pharmacological effects (Fig. 4).

4. Discussion

It is crucial that risk managers prioritize food safety issues to ensure that limited resources are allocated for detection of the substances of the highest concern. In this study, we developed a risk-ranking system using a semi-quantitative method that was modified from that of the VRC [19]. The available toxicological data and probability of exposure were integrated to calculate the risk score for ranking pesticides according to the health risk they pose, with postmarketing data from Taiwan employed.

Various risk-ranking methods are available for identifying potential risks through attribution of exposure and hazards or other factors [22]. These methods have been developed using qualitative or quantitative methods, depending on their purposes, time, data availability, and the risk manager's requirements. An example of a quantitative method is comparative risk assessment [23], which assesses risks through hazard identification, exposure assessment, hazard characterization, and risk characterization. Although this quantitative method provides detailed information through uncertainty and variability analyses, it requires considerable resources and high-quality data. However, when limited data are available or when there is an emergent situation, more qualitative methods can be used for risk ranking. The flow chart (decision tree) [24] was developed based on a set of defined questions or criteria to classify chemical hazards into different categories (e.g., high-, medium-, or low-risk) according to their impact on human health. However, this method requires considerable expert input and requires elicitation of the experience of these experts. Moreover, such an approach lacks transparency with respect to the classification of chemicals into high-, medium-, and low-risk categories. In the present study, the scoring system was developed based on a semi-quantitative concept; multiple factors for severity and

Table 2 – Five highest risk scores, individual factor scores, and the corresponding pesticides.

Pesticides	Factors				Total score (A + B) × C × D
	(A)	(B)	(C)	(D)	
Dithiocarbamates	5	3	4	4	128
Endosulfan	4	3	4	4	112
Carbofuran	5	4	4	3	108
Bromopropylate	5	3	4	3	96
Chlorothalonil	5	3	4	3	96
Chlorpyrifos	5	3	4	3	96
Cypermethrin	5	3	4	3	96
Fenvalerate	5	3	4	3	96
Fipronil	4	4	4	3	96
Flusilazole	5	3	4	3	96
Iprodione	5	3	4	3	96
Procymidone	5	3	4	3	96
Propargite	5	3	4	3	96
Tebuconazole	5	3	4	3	96
Thiamethoxam	5	3	4	3	96
Clofentezine	4	3	4	3	84
Difenoconazole	4	3	4	3	84
Ethion	4	3	4	3	84
Famoxadone	4	3	4	3	84
Fluopicolide	4	3	4	3	84
Hexaconazole	4	3	4	3	84
Propamocarb hydrochloride	5	2	4	3	84
Propiconazole	4	3	4	3	84

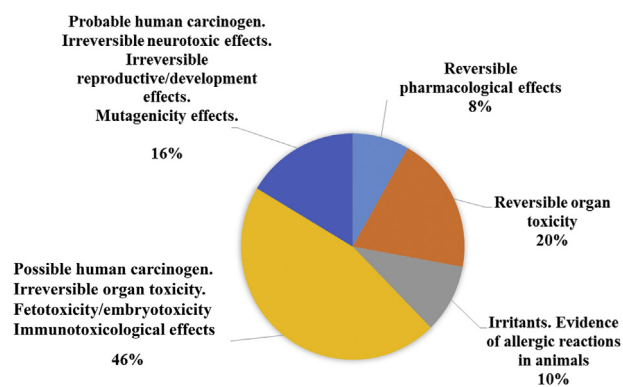


Fig. 4 – Percentages of endpoints in nature of hazard (factor A).

probability of exposure were used and combined to obtain a risk score for ranking pesticides. Compared with quantitative and qualitative methods, the semi-quantitative method employs various factors, including quantitative and qualitative data [22]. Furthermore, this method is more flexible and has higher ease of communication than other methods. Our study identified the pesticides present in several types of food products that warranted the most stringent monitoring, allowing a risk manager to instantaneously consider the possible risk management strategies and design a risk-based monitoring program. Our study was based on model calculations; however, further validation is warranted by comparison with the results of inspections.

Sensitivity analysis aimed to identify which factors have greater contribution to the ranking than the others, however, the data limitations might have great influence on the results of analysis. The scores of factor B and D for most pesticides included in our data were the same (score 3), leading to the less contribution of factors B or D to the ranking score. The ADIs of most pesticides in our study were between 0.001 and 0.1 mg/kg-d (factor B = 3), and most of them were violation (factor D = 3). The score of factor D represented the legal situation of pesticides detected in crops, and data of compliant pesticides were not included in our present study. This scoring system is adopted from the system for scoring veterinary residues in food in the UK [19]. Therefore, based on the available data, the scoring principle for factor B and D could be redefined in the future.

Dithiocarbamates, endosulfan and carbofuran were identified as the pesticides of highest concern because the highest nature of the hazard (factor A) scores were obtained for these pesticides. The dithiocarbamates considered by the JMPR and Codex which consist of several pesticides are all determined by a method depends upon the generation of carbon disulfide (CS₂), including amobam, cufraneb, ferbam, mancozeb, maneb, metiram, propineb, thiram, ziram, and zineb [25]. Macozeb, maneb, metiram, propineb, and zineb were reported to induce thyroid toxicity based on evidence of thyroid follicular hyperplasia with increased size, thickening, and weight of the organ in an animal study [25]. Also, zineb was discovered to be teratogenic in mice [25]. Furthermore, the violation rate and consumption of dithiocarbamates are high in agricultural products; therefore, these pesticides also had a

high score for factor C. Our results are consistent with the 2015 EU annual report on the risk assessment of pesticides residues in food [3]. According to the EFSA report, residues of five types of dithiocarbamates: maneb, mancozeb, propineb, thiram, and ziram—were detected in food. The calculated exposure exceeded the toxicology reference values (i.e., the acute reference dose [ARfD]) for three of the five pesticides (maneb, propineb, and ziram). Moreover, it should be noted that endosulfan, the second identified pesticide in our results, has been banned in Taiwan in 2014. Endosulfan is still presented in our samples because the data was collected before the ban. An EFSA report [26] stated that several banned pesticides were detected in concentrations greater than the MRL in crops in 2010 (i.e., acephate, dichlorvos, endosulfan, fenpropathrin, fenthion, hexaconazole, and procymidone), and long-term exposure to these pesticides may pose a high health risk. These pesticides are still used in several third-world countries. Endosulfan is classified as being of medium concern for animal and plant products based on its toxicological profile and the occurrence of residues in samples from the EU residue monitoring programs [26]. Carbofuran has a very low ARfD (0.00015 mg/kg body weight), and the ARfD was exceeded by high percentages (420%–567%) according to a report by EFSA in 2015 [12]. The dominant source of carbofuran presented in crops could be metabolites of carbofuran and benfuracarb, instead of from application of carbofuran. Therefore, these pesticides should be frequently monitored in postmarketing monitoring programs because of their severe toxic effects and high detection rate in monitoring programs.

Approval must be obtained for the sales and distribution of pesticides from the Agropesticides Management Act in Taiwan. The users of agropesticides can employ those approved by a central competent authority. If a crop's pesticide residue exceeds the standard stipulated by the competent health authority before appearing on the market, the crop or its product are re-examined or reinspected until they meet the standard. However, some pesticides were excluded from our study because of a lack of toxicity data. For example, oxycarboxin, prothiofos, and tetramethrin were assigned with a high score for probability of exposure because these compounds are frequently detected in the selected agricultural products; however, no ADI was assigned. One of the detected pesticides in our monitoring program was omethoate, which has been found to have genotoxic and mutagenic effects, but its ADI has been withdrawn because the primary manufacturer discontinued its production in 1996. Although these pesticides were excluded from our risk-ranking system, they may still be present in crops. Further research is needed for improving our scoring system by including these pesticides, which may have a high toxic potential (e.g., carcinogenic and genotoxic potential in animal studies) but not an established ADI. This reveals that the systematic approach followed in this study not only enabled the identification of pesticides of high concern, but also revealed the data gaps that warrant further attention.

In order to protect the consumers health, the result of pesticide risk ranking can be used by the authority of government to adopt corresponding measures, such as review and evaluation of those high-risk pesticides again, providing

pesticide training courses for the pesticide offenders, restriction of the use of highly prioritized pesticides, and replacement of the highly prioritized pesticides with safe substitute chemicals when it is available.

The proposed risk-ranking system and underlying data source have several limitations, leading to uncertainties in the risk ranking of pesticides. First, the nature of the hazard (factor A) for pesticides was well established, based on the data available from animal studies; however, score assignment by experts opinions might cause the uncertainties between evaluation results from different experts. Second, ADI (factor B) may be an appropriate indicator that reflects the potential adverse effects of a substance on human health; however, some pesticides without ADI values (because of insufficient toxicological information) cannot be ranked using our risk-ranking system, leading to a data gap in estimating potential highly toxic pesticides. Third, in the case of the exposure factor (factors C and D), only data for the non-compliant samples were available in the postmarketing program of Taiwan. Information for samples containing pesticides at or lower than the MRL is unavailable. Only non-compliant pesticides were analyzed in our study, which limited this study to several high-concern pesticides. Therefore, this data limitation would underestimate exposure.

In summary, the risk-ranking method used in this study allowed the classification of pesticides as those with high or low concern for monitoring. This, in turn, helps in the prioritization of pesticides according to their risk rank, enabling efficient resource utilization in monitoring programs that can then focus on the highly concerned compounds. However, some uncertainties shall be noted or improved in the future, including the difference in experts opinions (for factor A), the problem of pesticides without ADI (for factor B), and incomplete data without compliant pesticides (for factor D).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jfda.2018.06.009>.

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