Letter to the Editor

Methodology and Application for Health Risk Classification of Chemicals in Foods Based on Risk Matrix*

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The method has been developed to accurately identify the magnitude of health risks and provide scientific evidence for implementation of risk management in food safety. It combines two parameters including consequence and likelihood of adverse effects based on risk matrix. Score definitions and classification for the consequence and the likelihood of adverse effects are proposed. The risk score identifies the intersection of consequence and likelihood in risk matrix represents its health risk level with different colors: 'low', 'medium', 'high'. Its use in an actual case is shown.

The Food Safety Law of the People's Republic of China, which came into force in June, 2009, lays down that 'the State shall establish a food safety risk assessment system to assess the risks of chemical, biological and physical hazards in food and food additives'. Over the past five years, China has launched multiple food safety risk assessment actions, during which risk assessment approaches are gradually applied to food safety field. However, there still exist several crucial scientific questions when we carry out food safety risk assessment, two of which are how to accurately identify the magnitude of risks and how to use uniform and standardized terminologies to objectively describe the degree of risks. It is necessary to adopt a standardized method for health risk classification of chemicals in foods to describe the results of risk assessment. And it is also useful for risk management and risk communication to understand what the degree of risk means. So far, there was no universal methodology for health risk classification of food chemicals. The Risk Ranger tool developed by the Australian Food Safety Centre was in Microsoft Excel spreadsheet software format semi-quantitative model for food product/hazard combination ranking in 2001[1]. Through a cooperative agreement with the U.S. Food and Drug Administration, the Institute of Food Technologists developed iRISK, which was a web-based, interactive risk assessment tool that to enable comparison of microbiological and chemical hazards in foods[2]. For a specific hazard-food combination the model could produce a single metric: a final risk value expressed as annual pseudo-disability adjusted life years (pDALY). However, the methods which were developed by above authors are not suitable for chemicals risk assessment of food safety in China because the parameters are too complex and some of these parameters can't be described due to lack of data. Risk matrix is a qualitative and quantized analytic method. It often is applied to a risk management project to identify risks and management effects for project assessment[3]. As early as 1995, risk matrix was used in Electronic System Center (ESC) of American air force for weapon system research project[4]. Historically, Risk matrix model has been used in engineering, transportation, and environment sciences[4]. To use the risk matrix, we need to build a risk matrix; A risk matrix assigns a unique decision to any risk. It presents a two-dimensional table of decisions. Row of risk matrix corresponds to consequence and column of risk matrix corresponds to likelihood. In present study, this risk matrix model is used to design a risk classification method which could be applied to chemicals risk assessment of food safety in China.

Google (Taiwan) as a search engine used in the risk classification status at domestic and abroad. Retrieve the key words were risk ranking & food; risk classification & food; chemical hazard; risk matrix;

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acute toxicity; genotoxicity; subchronic toxicity; subchronic toxicity; chronic toxicity; carcinogenicity; reproductive toxicity; developmental toxicity; neurotoxicity; immunotoxicity, etc. Retrieve the web sites are: http://www.cnki.net/; http://www.moh.gov.cn; http://www.ncbi.nlm.nih.gov/pubmed; http://www.fda.gov/; http://www.who.int/; http://www.fao.org/index_en.htm; http://www.inchem.org/; http://www.iarc.fr/; http://ec.europa.eu/; http://www.epa.gov/raf/; http://www.standards.co.nz/, etc.

Expert panels were invited to take part to identify and select the most relevant parameters and indicators. A total of 51 experts were from Food Safety Risk Assessment (18), Toxicology (12), Public Health (16), Health Statistics (3), Food Chemistry fields (2). The panel discussed several key questions such as key parameters, indicators system for health risk classification of chemicals in foods and their relative importance. After three expert meetings, the panel followed a holistic approach to evaluate the most important indicators for health risk classification of chemicals in foods and their relative importance.

The chemicals health risk classification of the risk matrix framework and its indicators system are built based on relevant reports in the literature, given risk assessment cases and expert judgment. Codex Alimentarius defined risk as 'a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food'. Therefore, consequence and likelihood of adverse effects are key parameters used to evaluate a risk in this health risk classification system. A 5 x 5 matrix was chose by expert opinion in this study. To build a risk matrix for health risk classification of chemicals in foods is normally conducted in three steps as following: (1) determining the consequence severity; (2) determining the likelihood of adverse effects when exposure to a hazard; and (3) determining the risk level[4]. In the first step, the consequences that can occur in risk identification and how the consequences will be measured in the risk matrix should be considered. In principle, consequence severity is generally determined by consideration such indicators as hospitalization rate and prevalence rate caused by a hazard in an incident[5]. However, when it comes to chemicals like regular environmental pollutants and food additives, such data as hospitalization rate and prevalence rate is normally not available. In this case, toxicity or severity of adverse effects can be used to measure consequence resulted from a chemical[6]. The severity scores are measured using toxicity of adverse effects of a given chemical including acute toxicity and long-term toxicity should be considered jointly. After reviewing these reports from the web sites mentioned above, we can get existing scientific evidence for acute toxicity and long-term toxicity. Acute toxicity is expressed in 'rat oral lethal Dose 50 (LD_{50})' (represented by 'Ha'). Pursuant to China's GB15193. 3 Acute Oral Toxicity Test (draft for comment), which is currently under revision, acute toxicity may be classified into 5 categories. The categories of acute toxicity are given on a scale from 1 (Lowest) to 5 (Highest) as shown in Table 1[7]. Long-term toxicity (carcinogenicity, mutagenicity, reproductive toxicity, neurotoxicity, chronic toxicity and sub-chronic toxicity are expressed in various toxicity category indicators (represented by 'Hb'). According to International Agency for Research on Cancer (IARC)'s evidence-based principle for weight determination, carcinogens are classified into 5 categories, which are given on a scale from 1 (Lowest) to 5 (Highest) as shown in Table 1; According to the EU criteria for mutagenicity and reproduction classification, mutagenicity and reproduction of chemicals could be classified into three categories (Table 1); According to the Environmental Protection Agency (EPA) criteria, neurotoxicants are classified into four categories (Table 1); According to Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification method for specific target organ systemic toxicity-repeated exposure, substances with specific target organ toxicity are classified into two categories (Table 1). When a compound had a variety of long-term toxicity, we would choose the assignment highest score toxicity indicator to describe the consequence severity according to the risk assessment conservative principle.

In this study, the weight coefficients of acute toxicity and long-term toxicity were determined by expert judgment. Normally, the weight is the same. But in the particular case acute toxicity and chronic toxicity weights will be different, depending on what the assessor to focus more toxic. In other words, the assessor can judge the hazard occurring based on given examples or scenarios. Hence, formula for calculating consequence score of adverse effects was:

Overall Score of consequence=(Score Ha+Score Hb)/2 (1)

Note. A fractional score is rounded up to the nearest integer.

The overall scores of indicator of consequences, which are assigned to scale from 1 to 5, correspond to the 'insignificant', 'minor', 'moderate', 'major', and 'severe', respectively. In the second step, the probability of the adverse effect occurs and how the consequences will be measured in the risk matrix should be considered. Due to lack of foodborne disease data, we selected the indicators of likelihood based on the experience and judgment of risk assessment experts in this study. Risk is defined as the probability that exposure to a hazard will lead to a negative consequence, or more simply, Risk= Hazard×Dose (Exposure)[8]. Thus, a hazard poses no risk if there is not exposure to that hazard. Therefore, the probability of the adverse effect occur was depended on the estimate of human exposure. The exposure and dose-response data concerning a given chemical could be used to estimate its chance to cause health impacts. HBGV is an important quantitative indicator for hazard characterization of chemicals in foods. It is commonly recognized that dietary exposure greater than HBGV may lead to a greater chance to adverse effects[8]. Therefore, it is reasonable that 'the ratio average exposure to HBGV in target population' is deemed as a key indicator (Pa) for determining the 'likelihood of adverse effects'. The bigger that ratio is, the greater the likelihood it represents adverse effects. Based on the value of the ratio, the indicator (Pa) is classified into 5 categories, which were given on a scale from 1 to 5 as shown in Table 2. In addition, the scope of impacted populations, measured by the 'percentage of populations with individual exposure levels exceeding HBGV' (Pb), should also be considered when determining the likelihood caused by a chemical. It was also regarded as an important factor. The probability of exceeding HBGV was also estimated for population as the percentage of individuals with an exposure dose above HBGV. For the likelihood, the overall scores are also assigned to scale from 1 to 5, correspond to the 'rare', 'unlikely', 'possible', 'likely', and 'almost certain', respectively (Table 2). Normally 'Pa' and 'Pb' are deemed to have same weight based on the expert judgment except for different in the particular case. Hence, formula for calculating likelihood scores:

$$\text{Overall Score of likelihood} = (\text{Score Pa} + \text{Score Pb})/2 \quad (2)$$

Note. A fractional score is rounded up to the nearest integer.

Table 1. Score Definitions and Classification for the Consequence of Adverse Effects

(Ha)* Rat Oral LD_{50} (mg/kg·BW)	(Ha) Score	(Hb)* Long-term Toxic Effect/Hazard Category	(Hb) Score	Overall Score	Consequence of Adverse Effects
<1	5	Carcinogenicity (Group 1); Mutagenicity (Category 1); Reproductive Toxicity (Category 1); Neurotoxicity (Category 1)	5	5	severe
1-50	4	Carcinogenicity (Group 2A); Mutagenicity (Category 2); Reproductive Toxicity (Category 2); Neurotoxicity (Category 2); Chronic toxicity (Category 1)	4	4	major
51-500	3	Carcinogenicity (Group 2B); Mutagenicity (Category 3); Reproductive Toxicity (Category 3); Neurotoxicity (Category 3); Chronic toxicity (Category 2)	3	3	moderate
501-5000	2	Neurotoxicity (Category 4); Carcinogenicity (Group 3)	2	2	minor
>5000	1	Carcinogenicity (Group 4); Uncertain health hazard effects, uncategorized toxic or hazardous substances, as well as those not categorized as toxic or hazardous.	1	1	insignificant

Note. *One of the two indicates for the consequence of adverse effects could be independent to classify the health risk if the data were insufficient in particular cases.

It is noted that one of the two indicators in consequence or likelihood could be independent to classify the health risk if the data were insufficient. However, the uncertainty of risk assessment would increase.

In previous studies, there were different ways of expressing risk such as probability, numbers of adverse outcomes, Disability Adjusted Life Years/The quality-adjusted life year (DALYs/QALYs) and scores[9]. In this study, a final risk score is presented in risk matrix, expressed as scores, combining the intersection of consequence and likelihood. The risk score identifies the intersection of consequence and likelihood in risk matrix representing its health risk level: 'low', 'medium', 'high'. Different colors represent different risk levels, different measures can be taken (Figure 1).

We applied the method in an actual case of determining the potential health risk level of dietary Trans fatty acids (TFA) intake in Chinese teenagers. TFA, like saturated fatty acids (SFA), raise LDL (or 'bad') cholesterol levels in the blood, thereby increasing the risk of coronary heart disease (CHD). However, TFA belongs to those not categorized as toxic or hazardous, the score for the consequence of adverse effects is 1. The level of potential consequence of adverse effect is 'insignificant'. Dietary Reference Values (DRVs) aimed at reducing the risk of cardiovascular diseases and in promoting cardiovascular health was that diets should provide a very low intake of TFA, that is, less than 1% of total energy intake recommended by WHO in 2003. According to results of the Risk Assessment of Dietary Trans Fatty Acids Intake in Chinese Population (Technique Report No. 2012-002)[10], the ratio average exposure to DRVs in target population (Pa) ranged from 0.1 to 0.5. Therefore, the score of Pa is set to 2. The percentage of teenagers with individual exposure levels exceeding DRVs (Pb) was less than 5%. Therefore, the score of Pb is set to 1. So, the overall score of likelihood of adverse effects is 2, indicating that the likelihood level is 'unlikely' in risk matrix. Combining the levels of consequence and likelihood in the risk matrix, the horizontal axis and the vertical axis intersects at a light green block (Figure 1). Therefore, the health risk level of dietary TFA intake in Chinese population is low.

Table 2. Score Definitions and Classification for the Likelihood of Adverse Effects

(Pa)* Weighted Ratio Average Exposure to HBGV in Target Population	(Pa) Score	(PB)* Weighted Percentage of Populations with Individual Exposure Levels Exceeding HBGV(%)	(Pb) Score	Overall Score	Likelihood of Adverse Effects
≥1	5	≥50	5	5	Almost certain
0.8-1	4	20-50	4	4	likely
0.5-0.8	3	10-20	3	3	possible
0.1-0.5	2	5-10	2	2	unlikely
≤0.1	1	≤5	1	1	rare

Note. *One of the two indicates for the likelihood of adverse effects could be independent to classify the health risk if the data were insufficient in particular cases.

Likelihood (overall score)	Consequence (overall score)				
	Insignificant (1)	Minor (2)	Moderate (3)	Major (4)	Severe (5)
Almost certain (5)	Medium (5)	Medium (10)	High (15)	High (20)	High (25)
Likely (4)	Low (4)	Medium (8)	Medium (12)	High (16)	High (20)
Possible (3)	Low (3)	Medium (6)	Medium (9)	Medium (12)	High (15)
Unlikely (2)	Low (2)	Low (4)	Medium (6)	Medium (8)	Medium (10)
Rare (1)	Low (1)	Low (2)	Low (3)	Low (4)	Medium (5)

Figure 1. Risk Matrix.

Application of the method in an actual case has provided useful insights. It could quickly determine the risk level of importance. However there are some limitations of this method. The model is not applied to the chemicals without HBGV in food. In addition, the model is mainly based on expert judgment. Hence, some of the weighting factors employed in the model are arbitrarily derived.

In conclusion, the method developed at CFSA was designed to enable accurately identify the magnitude of risks of chemicals in foods. The illustrative case presented here indicates that the method could yield reasonably high levels of consistency and participant satisfaction.

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