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Review Article

Application of Toxicological Data for Chemical Risk Management in Food Safety; TTC Approach

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Abstract

Advances in analytical techniques emerged the chemical contaminants risks that exist for many years, although they are not known. In food safety, the starting point of risk management of contaminants is the toxicological data. The effective use of risk analysis methodologies based on these data can help the protection of human health. The starting point of the methodologies used in the management of contaminants in foods is whether the contaminants are genotoxic or not. For non-genotoxic chemicals, non-threshold risk management method and for genotoxic chemicals, threshold method is applied. Due to the production of new chemicals, every day and as the number of these chemicals reached up to hundreds, a bottleneck in the production of toxicity data has been appeared. To solve this problem, threshold toxicological concern (TTC) is developed for the chemical contaminants whose chemical structures are known but exposure to them is below the certain amounts. Additionally, toxicological data that will contribute to the preparations of the regulations for the future new risks, such as nanofoods, have been started to be produced.

Keywords: *Food Safety; TTC Approach; Cramer Decision Tree; Nanotechnology; Risk Management*

Introduction

Food safety is an essential public health issue all over the world. When it comes to risks in the management of food safety, there are 2 priority risk groups: i. Microbiological risk and ii. Chemical risk. These risks in food are major cause of illnesses. Toxicology is a science focused on chemical risk. The toxicological approach is that the chemical is dose dependent and the toxicity profile is very diverse. In the years when analytical methods were inadequate, the presence of chemicals could only be noticed after massive acute poisonings. A few examples of these, in 1858, Bradford sweets (peppermint with arsenic) poisoning; in 1900, poisoning with arsenic-tainted beer (arsenic entered the supply chain through impure sugar which had been made with contaminated sulphuric acid) in England; poisoning with contamination of rice washing water with cadmium (cadmium from the mine); in 1950, mercury poisoning with fish as a result of industrial pollution in Japan; in 1955, milk powder inadvertently contaminated with sodium arsenate in the disodium phosphate additive [1]. Level of risk reduction is not always satisfactory in traditional food safety system which includes reactive approach, main responsibility with government, no structured risk analysis, relies on end product inspection and testing. Nowadays, modern food safety system includes preventive approach, shared responsibility, addresses farm-to table continuum, science based, use of structured risk analysis, establishes priorities, integrated food control and relies on process control. Therefore, this system provide facility that level of risk reduction is more improved [2].

Nearly 40 years ago, only mg-level measurements could be made by using analytical analysis methods. Nowadays, instrumental analysis methods have developed and organic molecules with developing analytical methods such as Gas Chromatography-Mass Spectrometry (GC-MS) and Liquid Chromatography-Mass Spectrometry (LC-MS) assess and heavy metals can be measured in ppt (part per trillion) levels with inductively coupled plasma mass spectrometry (ICP-MS) method. Thanks to the developing instrumental analysis methods, we know that thousands of organic biosynthesis products and natural chemicals are in foods, and it is known that more than 1000 chemical pollutants can contaminate foods. With the development of analytical methods, many food contaminants have been detected since the early 1960s. For example, Acrylamide is classified to International Agency for Research on Cancer as a Group 2A, it is a possible human carcinogen (IARC, 1994) [3,4]. It is formed more than one way. Generally, it is formed during heating starch-rich foods at high temperatures. The most important way is the Maillard reaction which is formed by the reaction of reducing sugars with the asparagine amino acid at high temperature [5]. If we leave natural chemicals aside, we are exposed to thousands of chemical contaminants. Today, these sensitive analytical analyses we know that there is no food with zero chemicals. It is the subject of toxicology to know how these chemicals, which are exposed to small amounts that do not show acute toxicity, will show a toxic effect through various mechanisms in long-term exposure. The practical result of these studies is the determination of amounts that will not harm even if exposed. So, the next problem is; in what quantities and how much are we exposed to these chemical pollutants depending on food consumption? Does the amount of exposed chemicals have a negative effect on health? If so, what effect does it have? Risk assessment methodology is applied for it.

Risk analysis

New science-based approaches to food safety provide an effective way. These approaches protect from chemical and microbiological pollutants which cause foodborne disease. They help to plan suitable measures when necessary [6]. Toxicologists have focused on and more concerned with substances on higher human exposures and reactive functional groups. Except for these substance, in risk analysis, there have been limited attempts the integration of data from the exposure and structure-activity relations to risk analysis. Risk analysis is an approach that helps detect safe vulnerabilities and determine safety levels and facilitates the determination of risk to human health. In order to understand the risk assessment steps 1 and 2 presented below, data belonging to the toxicity are needed to understand the toxic effects of a chemical on human health. This data can be obtained in 3 ways. These ways are: a) *In vitro* toxicity tests (at tissue and cell level), b) Toxicity tests with experimental animals and c) Epidemiological studies (with groups of people if there is previous exposure).

Risk assessment:

1. Hazard identification.
2. Dose-response assessment.
3. Exposure assessment.
4. Risk characterization [7].

According to the data we have obtained, we can talk about 2 types of chemicals which are important in risk assessment. These chemicals have genotoxic effect and non-genotoxic effects. Chemicals without genotoxic effect (threshold effect): The aim of toxicology is to find the appropriate threshold or safe level of a chemical considered to be no hazard to humans. Different definitions are available in connection with genotoxic effects for threshold. Threshold is the value or level reached before the adverse effect/toxicity occurs. For most toxic effects caused by a chemical, there is an exposure threshold at which an adverse effect does not occur [8].

Genotoxic (cancer-making) effective chemicals (non-threshold effect): Acceptable risk is the risk of cancer seen in one person out of every million (depending on this chemical) during his lifetime (70 years). Today, this value can be found with chemical-cancer risk calcula-

tions [9]. Day by day, thousands of chemical substances occur in food as natural or as a contaminant (especially during cooking). We cannot ignore them. However, new approaches are needed to avoid wasting time on trivialities. Frawley proposed the concept of a threshold level of intake giving a negligible risk for chemicals without toxicity data. It is low enough to cause no discernible risk and safe level [10]. This approach is a risk assessment tool that is based on the principle of establishing a human exposure threshold value for chemicals and provides spending more time/prioritizing high toxicity chemicals and rapid assessment of low-level exposures without testing [11]. Substances for this approach to be applied safely, there must be strong exposure data (how much, how much exposure). TTC is used for food contact materials and flavoring agents. It is recommended to use TTC in pharmaceutical impurities, cosmetics and herbal products. Application of TTC generally apply for oral exposure, dermal and inhalation exposure routes are given less attendance.

Why TTC approach

It can be briefly listed the factors that cause the TTC approach as follows:

- Determination of very low quantities with the rapid development of analytical measurement possibilities [12].
- Exposure to very low doses is generally considered harmless.
- The time and attention devoted to a particular substance should be commensurate with the health risk posed by the chemical (Don't waste time on harmless).
- Limited toxicological information is available in toxicity testing and safety assessment.
- It is desired to reduce the use of experimental animals.
- It is possible to analyze existing toxicity data to make predictions about the behavior of chemicals with similar chemical structures [12-14].

John Frawley (1967) suggested a generalized human exposure threshold for chemicals is not new approach. Frawley suggested that in 1967 and proposed concept a human exposure threshold using data from multiple chronic rodent studies from among several well-tested studies including food additives for food packing materials. He constructed a reference database not necessary toxicity studies and safety evaluation. He used 2-years rodent studies and tested 220 chemicals including food additives, industrial and consumer chemicals. He presented the no-observed-effect levels (NOAELs) for them and reported. Frawley (1967) reported that there was no compound which showed chronic toxicity evidence in database except heavy metals and pesticides (including acrylamide). This means that human consume safely any material provided the application of x100 safety factor for 100 ppm NOEL and food concentration not higher than 1 ppm. Frawley (1967) Munro., *et al*. (1996) classified non-carcinogenic substances into 3 classes according to their chemical structure using Cramer's Decision Tree. Chemicals were rat and rabbit orally and obtained 2941 NOEL values of 613 chemicals [15]. Cramer., *et al*. (1978) presented the decision tree is a guide to how and when to apply the TTC principle.

The decision tree is only applied for substances with a known chemical structure and low molecular weight as shown in the database. For example, it is not applied to polymers. A good estimation of uptake or exposure is important in the use of the decision tree, as it determines whether the TTC has been exceeded. The original Cramer decision tree consists of 33 questions Answered 'yes' or 'no' for each question leading to another question or to the final classification into one of the three classes (I, II and III) as below:

1. Class I substances having simple chemical structures, efficient modes of metabolism exist, suggesting a low order of oral toxicity.

2. Class II substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.

3. Class III substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups [16].

Step 1. Remove substances and chemical structures that are not adequately specified in carcinogenicity and toxicity databases to improve TTC values. Step 2. If the substance is not eliminated in step 1, it goes to step 2 and at this step, whether the substance is genotoxic or a possible genotoxic carcinogen is defined. Step 3. If the answer is "yes" in step 2, the substance carries a structural stimulus in terms of genotoxicity, and step 3 identifies these structures that are likely to be the most potent genotoxic carcinogens, such as aflatoxin-like substances, azoxy and N-nitroso compounds. Step 4. The strongest structures were removed in steps 2 and 3. Step 4 asks if the estimated intake of the substance exceeds the 0.15 ug/day (or 0.0025 ug/kg bw/day) TTC. The chemicals were grouped into three structural classes based on a "decision "approach. This decision tree was made of a total of 33 questions for which each is answered by "yes" or "no". Each answer led to another question or to a final classification into one of the three classes (I, II and III), reflecting a presumed low, moderate and significant toxicity. Human exposure thresholds of 1800, 540 and 90 μg/person/day were proposed for class I, II and III, respectively.

Bioaccumulative compounds such as TCDD and its analogues, especially polyhalogenated dibenzodioxins, dibenzofurans, and biphenyls, whose half-lives vary greatly in different species and proteins, because they cause allergies at low doses, and because they have significant uncertainties in their low-dose effects, TTC approach is not applied to substances with endocrine activity and nanomaterials. The application of new technologies to foods creates new risks [16].

Nanotechnology and food safety

The focus of discussion has often been nanofoods. Nanotechnology is not just in the food industry it is also used in building materials for electronics, medicine, water treatment, biology, biochemistry and machinery, new devices and techniques [17]. Nanofoods production uses nanotechnology facilities. Nanotechnology which is the technology that uses materials with a size of 1 - 100 nm provides advanced or completely new physical, chemical and biological properties by arrangement of atoms or molecules of materials smaller than 100 nm [18].

The global nanotechnology market size was valued at $1.76 billion in 2020. It is estimated to reach $1 trillion in 2015. The use of nanotechnology in the food industry is increasing rapidly. Market value of nanotechnology products in the food industry. In 2010, it reached $20.6 billion in 2010 and this rapid increase has continued until today. Smaller particle size increases surface area and volume. As this gives new physicochemical and biological properties and many features such as small size, high surface/mass and quantum properties, by taking advantage of these properties of nanoparticles, more durable packaging material in the food industry, products that help with improved storage conditions, contamination sensors, taste and consistency improvers, nanotech foods (used for taste, nutritional value, consistency and safety) and nano-barcodes are produced [19].

The discussion about nanoparticles is that they easily enter cells/membranes, easily cross the blood-brain barrier, accumulate in cells/tissues, interact easily by chemical reaction, transport, increase free radicals and ROS [20]. The requirement for specific safety tests and the absence of regulations were problems. However, these limitations are eliminated by the studies and security lines are determined with the regulations. Nanoparticles can target mitochondria, which can cause mitochondrial degradation and reactive oxygen species (ROS) are formed, respectively. Oxidative stress, which occurs due to excessive ROS formation, stimulates the overexpression of antioxidant enzymes to control the ROS level [21]. At high levels of oxidative stress, it causes inflammation and cytotoxicity, thereby inactivating antioxidant defense systems [22]. Oxidative stress also induces lipid peroxidation, protein denaturation, nuclear and DNA damage, and immune reactivity. Standardized methods designed for chemical toxicology have caused problems when applied to nanoparticles because of their unique physicochemical properties.

*In Vitro**	*In Vivo*
Cytotoxicity assessment-Colorimetric dyes/fluorometric dyes-interactions ROS measurement assay-interactions	Studies not appropriate to food consumption (High doses, single dose, acute toxicity studies)
Adsorption of growth hormone factor and foods in cell culture-non-specific indirect growth inhibition and cytotoxicity	There is limited long-term chronic studies
Cell-cell complex, cell-matrix interactions, hormonal effect	Material characterization is limited in most studies

Table 1: *Some prominent problems encountered in vivo and in vitro [23].*

Applying more than one toxicity method for risk determination of nanoparticles will give safer and more accurate results [24]. Therefore, it was difficult to compare data on safety/toxicity from different research groups. In order to determine toxicity and obtain safe data, joint studies and projects were carried out between laboratories and standardization between laboratories and methods. Collaboration of many fields of expertise (such as food, chemistry, environment, toxicology) is encouraged.

In regulation regarding new foods and their ingredients, new foods must be subjected to pre-market control, which will allow to identify potential risks associated with the use of NMs and nanotechnologies. In the EU regulation dated October 26, 2011, all contents should be stated by using the word nano in parentheses on the label of the nanotechnological product.

Conclusion

We should evaluate the developing new technologies and take advantage of the opportunities they offer to the society, but before applying the technology, we must determine the limits for protecting human health and the environment with laws. We should inform and inform the public of every stage of the new technology without causing problems arising from the risk miscommunication that we have experienced before.

Conflict of Interest Statement

There is no conflict of interest.

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