Challenges for advanced human risk-assessment of food-related chemicals

Yasushi Yamazoe
Professor Emeritus, Tohoku University
and
Senior Fellow, FSCJ

Classical Methodology of Risk Assessment

- Based on the effects of administration of target substances in animals, and based on the genotoxic effects on DNA,
- Food safety on human health has been evaluated from above results.

Why animal studies are required?

- While clear targets are anticipated for effectiveness evaluation, prediction of potential adverse effects (where and how) is difficult in toxicity studies.
- Dose-effect relationship in adverse effects needs to be clarified for risk assessment.
- Consequently, a data list of comprehensively studied toxicity became essential for implementing safety evaluation.

Unresolved Issues of Safety Evaluation

Increase in number of substances which require evaluation

- Increasing number of newly developed materials
- Positive list system…Only substances listed are allowed to use.

Trace substances

- For a toxicity study even such as flavoring, the large amount is necessary to test though it is used only a trace amount in the products.
- Besides the active ingredient, many are contained in natural products (mixtures)
- Impurities in synthetized compounds

Traditional additives with a long use history, but without systemic tests

Approach to evaluation of a toxicity without morphologic changes.

Historical Development of Assessment Methodology to Overcome

- In order to accelerate the evaluating health effects, approaches have been taken mainly from two points of view.

- One is from the viewpoint of exposure levels. An approach to specify an intake with substantially negligible effects based on the accumulated data from toxicity studies.

- Another approach is to generalize structure-activity relationship between structural characteristics of the target substance and characteristics of its biological effects and toxicity, considering the mechanisms for toxicity.

Exposure Levels and Toxicity

- The pioneering work by Cramer-Munro et al. suggested that an ingestion dose with non-detectable risk could be specified based on a uniform study at the individual level. This concept became internationally accepted except for few such as dioxins, botulinum toxin and endocrine disruptors….Such are exceptional substances linking to high affinity receptors.

- This means a dose, at which the biological effect is negligible, i.e. (substantial threshold dose), can be specified based on the data from studies on chronic toxicity, reproductive developmental toxicity and carcinogenicity for many substances exposed daily.

- Provided that uniform judgment is not applied to substances showing positive in genotoxicity study, since the concept of one-hit theory can not be excluded for carcinogenicity.

Concept of Substantially No-Observed-Adverse-Effect Level

- Biological effect from a substance in human environment is appeared, if any, through the sustained exposure of the certain level, except strong genotoxic-carcinogens and/or receptor ligands.
- In cases that a substance is of no concern for accumulation in biological tissues or a low metabolic rate (detoxification), potential toxicological risk is extremely low.
- Verification of the existing toxicity data indicates that a toxicity is not detected when the daily intake is below 1.5 μg/day, (called the threshold of regulation).

Toxicological Threshold of Concern

- Food ingredients contain many substances in trace amounts beside nutrients. However, risk assessments of these substances are not easy.
- In the case of flavoring, e.g. partial vaporization occurs at room temperature, as its characteristics. In addition, if a flavoring is prepared from a natural substance, the available amount for conducting usual toxicity study is limited.
- It is sometimes difficult to synthetize impuritieseven in synthetic additives or in residual pesticides, or some of those substances are unstable in its property.
- There is another case such as a substance eluted from container into the content, where the usual toxicity study can be hardly applied.
- As a response to these issues, use of TTC approach has been considered.

TTC Approach

- When a group of substances resembled in structures exhibit toxicity of similar profiles, toxic potency of an untested substance, resembled in structure, may be estimated using the structure effect relationship. Practically the strongest potency is applied as a quantitative estimation.

- On the basis of the pioneering work on flavoring by Cramer-Munro et al., subject of TTC approach is expanding.

Introduction of Mechanism of Action and Physiological Concept into Toxicity Evaluation

- Conventional knowledge of structure toxicity relationship was useful for hazard estimation, but was not applicable to risk analysis.
- Analysis of accumulated data of toxicity started to reveal the actual mechanism whereby a substance exerts toxicity.
- For a group of substances where toxicity is exerted as a class effect, read-across approach may be applicable. The read-across provides useful information to a quantitative evaluation (category approach) with consideration of accumulated data on the exposure of the target tissues and metabolism.
- As for human safety which is the aim of toxicity evaluation, human exposure can be estimated using pharmaco/toxico-kinetics, thus human safety can be assessed taking into consideration the validity of specie differences.
- Interspecies scaling through body-size, and other phisiological parameters called allometry is developing.

Re-use and Application of Toxicity Findings

Compiling Information of Toxicity Evaluation

- Information on chronic toxicity as well as poisoning (acute toxicity) becomes available.
- Information of developmental toxicity
- Cross searching function i*n silico* to verify mutual relationship between chemical structure and toxicity profile could be powerful tools.

Utilization of human medicinal products database

- Extraction of toxicity signs from human clinical test data
- Improved Human-Relevance

Key to the future

- Internationally harmonized understanding of *in silico* technology; How and Where to apply (e.g. mutually acceptable ranges of structural similarity in TTC)

- Ensuring reliance on the new technology among assessors, applicants and users