Scientific basis for risk analysis of food-related substances with particular reference to health effects on children

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ABSTRACT — Based on the advance of toxicology and related sciences, a regulatory regime for the safety of chemicals related to daily life has been rapidly established. Especially for the food-related substances, the process of risk analysis has facilitated the collaboration by all the players including consumers toward the security of their safety. On the other hand, except for pharmaceuticals, science-based decisions and governmental actions on safety issues have not always gained confidence of the public. One of the reasons was the inadequacy in the way of use of scientific knowledge, or in other words, inappropriateness of decision making by “the regulatory science”. Regulatory science is a science to warrant the decision making processes for governmental acts (Mitsuru Uchiyama). In the case of chemical safety, it can be redefined as a theoretical concept to complements the uncertainty of scientific knowledge for the decision of governmental acts that is adequate in both scientific and social ways. Therefore, the regulatory science is an indispensable discipline to effectively apply risk analysis. Here, the significance of the regulatory science for the hazard assessment of the chemicals, especially for children is described. In the past, the hazard effects of chemicals have been assessed for adults. Recently, however, the importance of the assessment for children has gained international emphases. Not only for pharmaceuticals, but for food-related substances, the acceptable daily intake (ADI) and tolerable daily intake (TDI) are often set differently for adults and children. The child-specific responses against chemicals are related not only to the physiological factors such as body weight, basal metabolism, but also rapid growth of the body with developmental status of various organs. General knowledge on these issues will be discussed mainly referring the World Health Organization (WHO) documents. Although the cutting edge technology backs up the development of toxicology, it would appear that it is reaching a turning point from technology-centrism to look toward the direction for contribution to society from the stand point of regulatory science.

Key words: Risk analysis, Regulatory science, Food-related substance, Children

INTRODUCTION

Ensuring a consistent supply of foods and energy is the essential requirement to perpetuate existence and prosperity of human being. In cooperation with food scientists, toxicologists have been contributing to resolution of various food safety problems, such as contamination of foods with toxic substances or hazardous microbes during production, distribution or storage; generation of hazardous substances during food processing; estimation of acceptable intake levels or tolerable intake levels of food-related substances for general population or highly susceptible population; or public concerns about foods derived from genetically-modified organisms.

With the outbreak of several food-born diseases including bovine sponge form encephalopathy (BSE), O-157E coli infection and excessive pesticides residues on importated vegetables, food safety issues have become a growing concern to many people. On May 23, 2003, the Parliament passed the Food Safety Basic Law to keep our foods safe in today’s dramatically changing environment. Under this law the Japanese Government decides and implements food safety policies in accordance with two fundamental principles, first, the precedence of protecting the people’s health and secondly, the application of risk analysis (Food Safety Commission Secretariat, 2003; Hayashi, 2004).

In consideration of this situation, the present article was described to illustrate scientific basis for risk analysis of foods and food-related substances focusing on specific...
topics related to health effects on children.

Outline of risk analysis

Risk analysis is defined (WHO/FAO, 1995) as a process consisting of three components, namely, risk assessment, risk management and risk communication (Fig. 1), and generally understood or practically applied as a comprehensive measure for food safety issues. The three components are also defined (WHO/FAO, 1995) as follows;

Risk assessment: The scientific evaluation of known or potential adverse health effects resulting from human exposure to foodborne hazards. The definition includes quantitative risk assessment, which emphasizes reliance on numerical expressions of risk, and also qualitative expressions of risk, as well as an indication of the attendant uncertainties.

Risk management: The process of weighing policy alternatives to accept, minimize or reduce assessed risks and to select and implement appropriate options.

Risk communication: An interactive process of exchange of information and opinion on risk among risk assessors, risk managers, and other interested parties.

Risk assessment is performed on the basis of scientific data mostly derived from toxicological studies or testings on the agent of interest. Therefore, toxicology is regarded as the driving force for the risk assessment and eventually for the risk analysis.

Procedures of risk assessment

Assessment of adverse health effects in human from exposure to a particular agent is proceeded according to 4 steps (WHO/FAO, 1995);

1) The first step which is referred to hazard identification entails the identification of potential adverse effects associated with exposure to the agent. Data of toxicity testings (single dose toxicity tests, repeated dose toxicity tests, reproductive and developmental studies and genotoxicity tests) are useful for this step.

2) The second step, hazard characterization is pertaining to the qualitative and quantitative evaluation of the adverse effects associated with exposure to the agent. A series of animal data derived from dose-response studies, toxicokinetic studies and mechanistic studies are collected to predict adverse effects of the agent in human.

3) The third step, exposure assessment indicates the qualitative and quantitative evaluation of the intake in human (daily intake, duration of intake, mode of intake). It may be useful to investigate into characteristics of exposed population such as population with large amount of intake or population of high susceptibility.

4) The fourth step, risk characterization is the final step to integrate hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely occur in a given population. More practically, risk characterization for foods or food-related

Framework of Risk Analysis

Risk Analysis: A measure for decision-making consisting of 3 elements; Risk Assessment, Risk Management, and Risk Communication.

1. Risk assessors and risk managers should clearly separate their duties (Functional Separation) keeping a close interaction between them.

2. All stakeholders should participate in the decision-making process through interactive exchange of information and opinion toward an agreement of the decision or understanding problems to be resolved.

Fig. 1. The key concept of the Functional separation should be the “sharing of a task according to their speciality” rather than “complete separation of the task into two independent authorizations”.

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substances is to answer one of the following questions;
(1) What intake level of the substance of interest can be considered as negative for risk to human or the risk to human is acceptable?
(2) What degree is the risk from of the substance at the daily exposure / intake level in human?

**Execution of risk assessment**

Risk assessment is a scientific procedure to assess or infer the risk level or risk profile on the basis of existing information. Therefore, the execution of any given risk assessment may be hampered by involvement of various uncertainties resulting from deficiencies or critical gaps in the necessary information (Hayashi, 2004).

On such occasions, plausible assumptions are made, taking these uncertainties into account, so that the assessment can be completed (Fig. 2). Therefore, risk assessment is regarded as a complex mixture of available data and assumptions based on prevailing scientific thought and/or data on related substances.

The assumptions made for execution of risk assessment are mostly related to extrapolation of animal data to the human situation. Followings are typical examples;
(1) Human is regarded as the most sensitive species to the agent of concern unless otherwise evidence has been obtained.
(2) Differences in susceptibility to chemicals among species or individuals are not greater than 10 times respectively. This assumption has been frequently used to determine a safety factor or uncertainty factor for establishment of acceptable daily intake (ADI) (Benford, 2000).

**Genotoxic carcinogens versus non-genotoxic carcinogens**

Regulatory decision on carcinogenic risk is usually made on the basis of a scientific thought that genotoxic carcinogens have no thresholds while non-genotoxic carcinogens have thresholds. However, it should be understood that this thought is an assumption formulated for regulatory decision-making. Actually, neither genotoxic carcinogens nor non-genotoxic carcinogens have been scientifically confirmed as having threshold or not. Genotoxic carcinogens are known to have an irreversible effect on the genetic cellular structure. Thus, even in small amounts, genotoxic carcinogens are assumed to have additive effects and therefore to subject individuals exposed to them to an incremental risk of developing cancer (WHO/FAO, 1995). Accordingly, it is feasible to assume that there is no threshold for genotoxic carcinogens. In contrast, non-genotoxic carcinogens are considered to act at extra-genetic sites, leading presumably to enhanced cell proliferation and/or sustained hyper-function/dysfunction at the target sites (Hayashi, 1992). Therefore, it is plausible to assume that a minute intake of non-genotoxic carcinogens will not result in any significant level of cancer risk (WHO/FAO, 1995). The assumption that no threshold exists for genotoxic carcinogens has been applied in the regulatory decision on the carcinogenic risk of food-related substances such as food additives, pesticides and contaminants. However, it must be known that many people misunderstand this assumption as an indisputable concept established on the basis of scientific evidence. A strong adherence to zero-risk can be
raised as an example of assertion derived from this misunderstanding. Actually, a large amount of scientific data has been reported to support the view that genotoxic carcinogens have threshold (Hayashi, 2005).

**Food-related adverse health effects and high-risk population**

Adverse health effects caused by intake of foods can be divided into following groups;  
1) Poisoning due to intakes of foods contaminated with pathogenic microorganisms.  
2) Poisoning due to intakes of altered, denatured on spoiled foods.  
3) Poisoning due to intakes of foods polluted with toxic substances such as methyl mercury or cadmium.  
4) Adverse health effects due to deficiencies of specific nutrients (thiamin, ascorbic acid or iodine).  
5) Adverse health effects due to excess intakes of specific nutrients (various lipid-soluble vitamins).  
6) Adverse health effects due to excess calorie intakes.  
7) Adverse health effects probably due to inadequate intakes of non-nutritive functional food constituents (various antioxidants).  
8) Adverse health effects in high-risk population.  

Recently, high-risk population has come to be considered as an important underlying factor when analyzing the occurrence of adverse effects associated with food intakes. It is necessary to understand that high-risk population includes various categories as follows;  
1) High exposure population such as high-level occupational exposure, environment-derived high-level exposure and high-level exposure to certain substances associated with a specific life style.  
2) High-susceptibility population.  
   (1) High-susceptibility due to certain genetic factor(s).  
   (2) High-susceptibility related to aging or specific life stage such as early development or delayed maturation.

**Susceptibility of children to environmental factors**

It has been thought that children are not simply small adults but rather are an unique population for health assessment (Guzelian et al., 1992). A recent document from the World Health Organization (WHO) describes children, who comprise over one-third of the world’s population, are among the most vulnerable of the world’s population and that environmental factors can affect children’s health quite differently from adult’s health. In this WHO’s document, the terms “children” and “child” are used to include the stage of development from conception through adolescence (WHO, 2006).

From fetuses, neonates, infants through adolescence, rapid growth and developmental process occur that can be disrupted by exposure to environmental factors. A series of such disruption is thought to act as an underlying mechanism for different susceptibilities during life stages.

Children are different in anatomical, physiological, metabolic, toxicokinetic, and behavioral process, for example;  
Children consume more food and beverages per kilogram of body weight than do adults;  
Children have a higher inhalation rate and a larger body surface area to body weight ratio than adults;  
Children’s metabolic pathways may differ from those of adults;  
Children have more years of future life and thus more time to develop chronic diseases that take decades to appear and that may be triggered by early environmental exposure.  

All these factors are also related to different susceptibilities of children. The accumulating data suggests that susceptibility depends on the substance and exposure situation. In some cases, there may be no difference in responses of children and adults. In other cases, different physiologically on metabolic factors, pharmacokinetics and diet on behavior patterns can render children more (or less) susceptible than adults.  

In the following sections, typical examples of different susceptibilities between children and adults during different development stages will be briefly described.

**Effects of fetal and early childhood nutrition on the occurrence and progression of cardiovascular diseases in adults**

Epidemiological studies indicate that babies who are significantly small at birth due to fetal malnutrition have higher risks of ischemic heart disease and type 2 diabetes in adulthood. On these epidemiological data, the fetal origin hypothesis of cardiovascular disease was proposed by Barker et al. (1993).

Later, Singhal reported interesting data that preterm neonates fed on nutrient-enriched formula for 4 weeks with the purpose of growth acceleration showed a tendency of obesity at 13-16 years of age assessed by test parameters such as blood lipid, blood pressure and insulin resistance (Singhal et al., 2001).

A series of animal experiments and clinical investigation have been conducted to determine which is relevant to health effects in later adult life, malnutrition at fetal stage or enriched nutrition at early infancy to stimulate catch-up growth.
Interesting results were obtained from a mouse study (Ozanne and Hales, 2004). Pups nursed by dams fed on low-protein diet resulted in restricted growth. They showed an increased longevity and the longevity was not shortened by obesity-inducing diet given after weaning. In contrast, pups born from low-protein-fed dams and raised with a standard laboratory chow (20% protein) or obesity-inducing diet exhibited a rapid catch-up growth and shorten longevity. These findings indicate a possibility that growth acceleration at early stage of infancy affects health status in later adulthood (Singhal and Lucas, 2004).

It is known that breast-fed children show faster growth in height, slower increase in body weight and smaller variance in growth patterns as compared to the international standard growth curve (Garza, 2006). Furthermore, breast-fed children are reported to show lower blood pressure than formula-fed children (Martin et al., 2005) and lower plasma cholesterol than formula-fed children (Owen et al., 2003).

All these findings support the view that rapid growth during neonatal stage adversely affects the life in adulthood, though the mechanism still remains unclear. Uncovering of gene-nutrient interaction will be the key to elucidate the mechanism.

Age-difference in bilirubin-induced cerebropathy (Kernicterus)

It is extremely rare that adult jaundice is associated with bilirubin precipitation in brain parenchyma. In cases of severe neonatal jaundice, particularly in preterm neonates, indirect bilirubin is frequently observed to precipitate in hippocampus, dentate nucleus, thalamus, hypothalamus, and olivary nucleus resulting in neuronal degeneration and brain dysfunction. Occurrence of “Kernicterus” is attributable to immature glucronic acid conjugation in the liver, insufficient blood-brain barrier, immature renal excretion and enhanced bilirubin production in preterm neonates (Guzelian et al., 1992).

Age-difference in neurotoxicity of cholinesterase inhibitors

Animal experiments in rats indicate that there is age-difference in neurotoxicity of cholinesterase inhibitors and the sensitivity as assessed by mortality, behavioral changes and brain cholinesterase activity is shown to reduce with post-natal days. For example, neurotoxicity is shown to appear at lower levels of exposure in 3-weeks old rats than those in adult rats. Vidair estimates the ratio of toxic levels for adult rat to those for 3-weeks old pups as follows (Vidair, 2004);

- Chloropyriphos 2-5 folds
- Malathion 4 folds
- Aldicarb 2 folds
- Methamidophos almost same

From the viewpoint of brain development, rat at 3 weeks of post-natal age corresponds to newborn infants in human (Bayer et al., 1993). Sensitivity to neurotoxicity of cholinesterase inhibitors in human is surmised to be higher in newborn infants than in adults although current database is insufficient. As a mechanism for lower sensitivity to organophosphates in adults than in newborn infants, it is known that the activity of inactivating enzyme (A-esterase, carboxyesterase) is higher in adults than in infants.

Susceptibility of children to lead

By comparison to adults, children are more vulnerable to lead in terms of exposure level and the lowest blood concentration at which adverse health effects occur occur. 1) Amount of exposure: children > adults (due to characteristics of children’s behavior).

2) Lowest blood level to cause adverse effect.

Effects on neurobehavioral development in children below 10 µg/dl.

Effects on behavior in adults 40 µg/dl.

Effects on peripheral nerve conduction velocity children 20 µg/dl, adults 30 µg/dl.

Anemia children 70 µg/dl, adults 80 µg/dl.

Decrease in hemoglobin children 40 µg/dl, adults 50 µg/dl.

Basic research to elucidate mechanisms of neurobehavioral development and its reversibility will be useful to construct scientific principles for regulatory measures for lead (Guzelian et al., 1992).

Occurrence of delayed abnormal estrus cycle in rats by perinatal administration of bisphenol A

High dose of bisphenol A has been known to cause no particular toxicity in adult animals. Recently, it was shown that oral administration of bisphenol A to dam rats from gestational day 6 to postnatal day 20 induced delayed abnormality in estrus cycling (persistent estrus) in female off-spring. Estrogen administration is known to induce abnormality of estrus cycling, indicating a mechanism mediated by estrogen receptor binding. It is known, however, that estrogenic activity of bisphenol A is only 10^8 of estradiol-17 beta, and the affinity of bisphenol A to estrogen receptor is 1/1,500 of that of estradiol-17 beta. Thus, there is a possibility that the delayed effect of bisphenol A is not mediated by estrogen receptor binding (Research report, 2004).
Evaluation of cancer risks in children by genotoxic carcinogens

1) General principle.
Carcinogenic risks from exposure to chemical substances are usually assessed on the basis of animal carcinogenic tests and epidemiological database of occupational cancers. However, it should be understood that both of these two methods are designed for adults. Therefore, consideration will be necessary to answer the question “Are the methods or concepts for adults applicable to the assessment of carcinogenic risks in children?”

Regarding genotoxic carcinogens, animal data from long-term carcinogenicity tests, carcinogenicity tests by administration at neonatal stage (neonatal carcinogenicity tests) and tests combined both neonatal administration and long-term administration are fairly well accumulated.

US·EPA has proposed to assess cancer risks of chemical substances in children based on the following principles using the above database (Barton et al., 2005; U.S. EPA, 2005);

1) Children are more susceptible to genotoxic carcinogens than adults.

2) Cancer risks in children can be estimated by application of age-dependent adjustment factors to the values relevant to cancer risks in adults. Following are age-dependent adjustment factors proposed by US·EPA.
Age 0-2 years factor 10.
Age 2-15 years factor 3.

2) Inorganic arsenic carcinogenesis by oral administration in mice.

Inorganic arsenic is confirmed as an important human carcinogen while no definite evidence of carcinogenicity has been shown in experimental animals.

Recently, a study indicated that the offspring of pregnant C3H mice given drinking water containing sodium arsenite (NaAsO2) at concentrations of 42.5 and 82 ppm ad libitum from day 8 to 15 of gestation developed hepatic, ovarian, pulmonary and adrenal tumors later in their lives (Waalkes et al., 2003).

This result suggests a possible existence of “Critical windows” during fetal development, although reproducibility of the experiment, strain difference, and mechanism of action has to be examined.

Finally, the author likes to quote a statement from a WHO document (WHO/FAO, 1995).

“The accumulating knowledge that children may be at increased risk at different development stages, with respect to both biological susceptibility and exposure has raised awareness that new risk assessment approaches may be necessary in order to adequately protect children. Traditional risk focused mainly on adults and adult exposure patterns, utilizing data from adult humans or adult animals. There is a need to expand risk assessment paradigms to evaluate exposure relevant to children from preconception to adolescence, taking into account the specific susceptibilities at each developmental stage. The full spectrum of effects from childhood exposures cannot be predicted from adult data. Risk assessment approaches for exposures in children must be linked to life stages.”

In summary,

1) Risk analysis consisting of 3 elements, namely, risk assessment, risk management and risk communication is a useful measure for ensuring safety of food and food-related substances.

2) Toxicologists are assigned for an important role in implementation of risk analysis, which includes, (1) Exchanging opinions with risk managers so that the result of risk assessment is properly reflected upon risk management; and (2) Setting assumptions to compensate for uncertainties due to an insufficiency of available data.

3) Accumulating evidence indicates that children are a specific subpopulation with high-susceptibility to environmental factors or a unique high-risk group, which needs to be considered in risk assessment.

4) For proper implementation of risk assessment in high-risk groups including children, it is necessary to challenge the following issues; (1) Construction of requisite database; (2) Establishment of assessment of methods based on existing data and prevailing scientific thought; and (3) Conducting basic research on the projects necessary to reduce uncertainties in risk assessment.

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REFERENCES


Risk analysis of food-related substance for children


