Commentary

Considering Risks of Food and Radiation
–Cancer Risk Assessment–

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There have been many discoveries of genotoxic carcinogens in food, as with radioactive materials, which are considered "carcinogens with no threshold." This paper presents a simple commentary on how such risks have been assessed.

I. Carcinogens in Food

Foods are "objects with an unknown chemical composition," which humans have been eating with the understanding that doing so does not cause immediate harm. Food additives and agrochemical residues are often topics of "food safety," and there are standards for their use and residual amounts with enough room to maintain safety. This might seem obvious, but the safety of food is not necessarily guaranteed. There can be some identified risks, but unknown objects made up the majority exist in a gray area. Due to the idea that food should be perfectly safe, which is an impractical idea, the general public might have a different way of looking at the risks from that of experts (**Figure 1**).

Representative examples of toxic substances in food include plant alkaloids in potatoes such as solanine and chaconine. When the inedible parts or globefish and mushrooms are eaten, poisoning can occur.

Substances such as solanine are commonly contained in food, though usually in concentrations too small to cause poisoning. Most toxic substances would not cause harm as long as the amount ingested is low, so they are not usually concerning; however, there are many cases of food poisoning caused by a lack of proper risk management based on the misunderstanding that natural products are safe.

Among toxic substances in food, genotoxic carcinogens cannot simply be neglected as something harmless if the amount ingested is low. Genotoxic carcinogens can cause cancer by affecting substances responsible for genetic traits such as DNA and chromosomes (genotoxicity). Typical examples include radioactive material, fungal toxins such as aflatoxin, and plant alkaloids such as aristolochic acid. Like radiation, genotoxic carcinogens are treated as materials whose risk is not zero unless the amount ingested (dose) is zero, i.e., there is no ingestion threshold in which safety is guaranteed. Therefore, substances that are intentionally

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used, such as food additives and agrochemical residues, are basically not allowed if they are suspected to be genotoxic carcinogens. Substances contained in natural food should be managed "as low as reasonably achievable" (ALARA).

This ALARA principle was somewhat meaningful when the number of genotoxic carcinogens in food was relatively low. However, scientists have continued to discover dozens of new genotoxic carcinogens (including candidates), and it is no longer realistic to simply apply the ALARA principle. A decisive moment occurred in 2002, when it was discovered that food products containing starches and amino acids produce significant amounts of acrylamide when heated to temperatures higher than 120°C. Acrylamide was a compound commonly known as an industrial chemical substance, but it was newly discovered that we ingest a significant amount of the substance on a daily basis. Acrylamide has been found to be carcinogenic due to animal experiments, and its mechanism is suspected to be genotoxicity. Acrylamide is not added to food but forms automatically during the cooking process, and food products constituting a substantial portion of diet have been found to produce the substance, including potato products, breads, cookies, coffees, and roasted green teas. It is impossible to "take as little as possible," and such an approach is inappropriate as it would make it difficult to maintain a healthy diet.

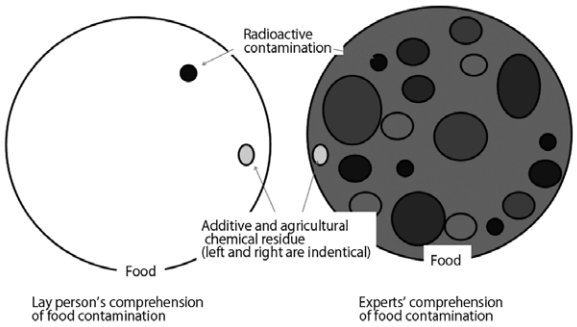

Figure 1 Views on food

II. Food Safety Risk Analysis

Food safety risk analysis has been used worldwide to ensure food safety [1)]. In 2003, the Food Safety Commission was established in Japan, and began conducting scientific assessments in regard to food safety independently from the Ministry of Health, Labour and Welfare and the Ministry of Agriculture, Forestry and Fisheries. **Figure 2** shows three elements of the risk analysis.

The Food Safety Commission conducts "risk assessments," and based on these assessments, the Ministry of Health, Labour and Welfare and the Ministry of Agriculture, Forestry and Fisheries work on "risk management" such as by setting standards and monitoring products in the market. The most important part of this effort is "risk communication" throughout the system. Risk communication should be carried out among all related parties, from suppliers to consumers; this does not simply refer to "briefing sessions," wherein the government unilaterally explains new standards to consumers. It is obviously important to understand the basic matters of communication, such as the problems and solutions, but that is not enough. To ensure food safety, it is important for all parties, from the farm to dining table, to take

responsibility and play their own roles (shared responsibility). For example, some food products are provided in edible form, and other products can be eaten safely only after cooking properly. Products such as raw meat can lead to health damages if the consumers do not appropriately store or cook them. Moreover, some food products might be safe as a single unit, but can lead to health damages when consumed in large quantities and for a long period. At the same time, few would argue that the government should determine the details in regard to when to eat, what to eat, and how much to eat, as done in animal experiments. Some countries and communities try to manage consumer selection by taxing food products with high sugar and fat contents. Risk communication involves a communication exchange among related parties to come up with the best solution for management methods. Consumers do not necessarily desire reinforced management because it can reduce options and increase consumer burden.

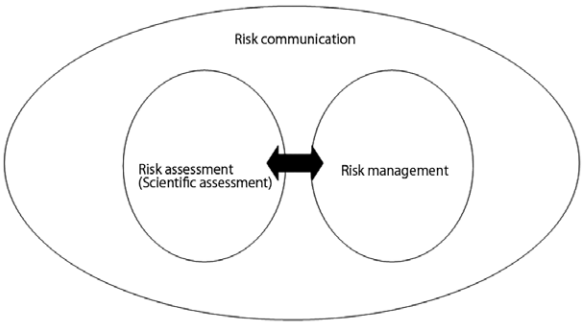

Figure 2 Conceptual map of risk analysis

III. Margin of Exposure

Risk communication is indispensable in food safety risk analysis. It is therefore necessary to educate the public on expert knowledge about the results of risk assessments and options regarding management methods. This task was particularly difficult for genotoxic carcinogens in food. In general, carcinogens are something to be avoided at any hand. Genotoxic carcinogens have been treated much like risk factors of radioactive materials; a linear non-threshold model has been used to extrapolate the results of carcinogenesis in humans and animals in the high dose range in order to create a slope factor (SF) (slope of the dose-response line), which is then used to calculate human lifetime cancer risk per exposure. In the field of setting environmental standards for chemical substances, a virtually safe dose is defined to range from 10^{-4} to 10^{-6}, and this range is used for management goals. The default value for sterilizer by-products in water is 10^{-5} (however, a realistically achievable value is set for inorganic arsenic, which is a natural contaminant, since this value cannot always be achieved).

Such a method has been used by experts as an indicator for risk assessment. However, human cancer risk 10^{-5} is often interpreted by the public as “one in 100,000 people can get cancer” or “if the Japanese population is approximately 100 million, 1,000 would die from cancer.” Given a lifetime cancer risk of 10^{-5}, one out of 100,000 is not the predicted number of people who will develop cancer; however, this misinterpretation is unavoidable, given the number.

To tackle the situation, the concept of margin of exposure (MOE) has been used as an

improved method for risk communication [2-4]. This is calculated by dividing an indicator dose of toxicity such as no-observed effect level (NOAEL) or benchmark dose lower confidence bound ($BMDL_{10}$) by actual human exposure. The resulting value is equivalent to the safety factor. In other words, this indicates how the actual exposure compares to the dose level at which harmful effects barely appear. The higher the value, the safer, and vice versa. An MOE lower than 1 indicates that the possibility of a harmful effect cannot be denied. Even if this number is indicated independently, it is impossible to tell how many people will develop cancer. It is only when the value is compared to those of other substances that it is defined as high, low, or same as the others.

MOE is an indicator for ranking priority in risk management. MOEs for several compounds can help determine which of them should be prioritized. **Table 1** shows the MOE values evaluated by the food safety organizations in countries across the world (a similar, though slightly different, table is shown in reference [5].

When exposure varies among individuals, it is possible to prioritize risk management based on the person's exposure and then MOEs, which will help consumers start thinking about their highest priority risks. They would also understand that genotoxic carcinogens have quite varying risks. For genotoxic carcinogens with an MOE higher than 1 million, countermeasures can be postponed even with the ALARA principle.

Risk analysis involves a concept called an appropriate (health and hygiene) level of protection (ALOP). This value indicates the acceptable target level of risk, and though it may vary from community to community, it should be defined for each society. Ideally, risk management measures are implemented to meet ALOP, but in reality, it is difficult to quantify the values. For example, it is easy to set a goal of having zero deaths from food poisoning, but this would require sanitary management for entire foods at the level needed for space food, which is impossible to implement. However, it would not be easy for the public to accept a calculated annual death rate of 1. From the viewpoint of risk psychology, it has been found that taking risks,even if it is negligible, is difficult. Risk ranking involves postponing goal setting and aims in order to deal with high or easy risks with a high cost-effect ratio, and subsequently if the task has achieved deal with the next risk in ranking. This is a practical method based on the risk-ranking measure. The protection standard of a country or community is set when such resources are depleted.

IV. Future Challenges

Carcinogen risk assessments are usually about the development of cancer or death from cancer. However, with the average life expectancy rising, it is debatable whether, for example, death from cancer at the age of 100 is a serious issue. It is meaningless to aim for zero deaths from cancer, so human cancer measures often aim to reduce the number of people of age 75 or under who develop cancer. Strong carcinogens can cause cancer in animals in early stages, but some weak carcinogens have, after animal experiments and during autopsies, been found to be precancerous lesions that can cause cancer if left alone. It is more desirable to appropriately evaluate the time factor, which would defeat the purpose of cancer measures if we were to invest only in cancer prevention and not as much on securing the lives of seniors. For example, if the average life expectancy were 40, many cancer measures such as non-smoking would not be necessary. Cancer would also not be of a particular risk. Lead, added to the end of Table 1, causes issues not in terms of cancer but child intelligence. Which should we

Table 1 MOE of genotoxic carcinogens

Substance	MOE	Condition	Organization, year
Benz (a) pyrene	130,000–7,000,000	Food source	COC, 2007
Hexavalent chromium	9,100–90,000	Food source	COC, 2007
Chrome	770,000–5,500,000	Drinking water	COC, 2007
1,2- dichloroethane	4,000,000–192,000,000	Drinking water	COC, 2007
Benz (a) pyrene	17,000,000–1,600,000,000	Drinking water	COC, 2007
1,2- dichloroethane	355,000–48,000,000	Indoor air	COC, 2007
Benz (a) pyrene	10,800–17,900	Food source	EFSA, 2008
PAH2	15,900	Average intake group	EFSA, 2008
PAH4	17,500	Average intake group	EFSA, 2008
PAH8	17,000	Average intake group	EFSA, 2008
Urethane	18,000	Non-alcohol	EFSA, 2007
Urethane	>600	Drinker of brandy and tequila	EFSA, 2007
Acrylamide	78–310	Indicator for rat mammary tumor	JECFA, 2010
Urethane	20,000	Average intake group	JECFA, 2005
Urethane	3,800	High intake	JECFA, 2005
Acrylamide	133–429	2–6 year-old children in Netherland	RIVM, 2009
Aflatoxin B1	63–1,130	2–6 year-old children in Netherland	RIVM, 2009
Furan	480–960	Food source	JECFA, 2010
Arsenic in food	Not safe	Average European consumer (Notes 1 and 2)	EFSA, 2009
Arsenic in food	1.1–33	Average French adult	ANSES, 2011
Arsenic in food	0.8–27	Average French child	ANSES, 2011
Acrylamide	419–721	Average French adult	ANSES, 2011
Acrylamide	261–449	Average French child	ANSES, 2011
PAH4	113,409–230,041	French adult	ANSES, 2011
PAH4	72,433–150,509	French child	ANSES, 2011
Inorganic arsenic	9–32	Average Hong Kong (Note 3)	CFS, 2012
Inorganic arsenic	5–18	Hong Kong High intake	CFS, 2012
PAH4	27,600–15,500	Average food origin for all English people - 97.5 percentile	EFSA 2008
PAH8	45,606	Adult	Spain, 2012
PAH8	40,078	Child	Spain, 2012
Arsenic	0.77–20.5 (Note 4)	Male	Spain, 2012
Arsenic	0.32–8.6	Child	Spain, 2012
Acrylamide	853–305 (Note 5)	Younger than 1 year old	Health Canada, 2012
Acrylamide	296–119	1–3 years old	Health Canada, 2012
Acrylamide	1,146–586	Older than 71 years old	Health Canada, 2012
Inorganic arsenic	3	Belgium adult	AFSCA, 2013
Inorganic arsenic	68	Belgium adult	AFSCA, 2013
Lead (Note 6)	0.9–1.9	Infant drinking only breast milk	COT2012 (proposal)
Lead	1.6–10	Infant drinking only milk	COT2012 (proposal)
Lead	1.3–5	Milk and baby food	COT2012 (proposal)
Lead	1.9–6.3	Water	COT2012 (proposal)
Lead	0.2–0.9	Soil	COT2012 (proposal)
Lead	100–833	Air	COT2012 (proposal)
Lead	3	Hong Kong, diet only	CFS, 2013
Lead	6	Hong Kong High intake, diet only	CFS, 2013
Lead	1.8–4.8	Belgium adult	AFSCA, 2013
Lead	0.5–1.2	Belgium child, 2.5–6.5 years old	AFSCA, 2013
Lead	1	Belgium infant, 3 months	AFSCA, 2013

PAH2: benz (a) pyrene, chrysene PAH4: benx(a) pyrene, chrysene, benz (a) anthracene, benz (b) fluoranthene PAH8: benz (a) pyrene, benz (a) anthracene, benz (b) Fluoranthene, benx (k) fluoranthene, benz (ghi) perylene, chrysene, dibenz (a,h) anthracene and indeno ((1,2,3-Cd)) pyrene

Note 1: Given $BMDL_{01}$ intake of 0.3–8 μg/kg weight/day, the estimate intake is 0.13–0.56 μg/kg weight / day

Note 2: Given $BMDL_{01}$ intake of 0.3–8 μg/kg weight/day, the estimate intake is 0.37–1.22 μg/kg weight / day.
People who eat seaweed might have 4 μg/kg weight/day, infants under 3 years old who eat rice have a value that is 3 times higher than that of adults

Note 3: POD used in Hong Kong was established in 2010 by JECFA. The inorganic arsenic intake in food in Hong Kong is half as much as that in Japan

Note 4: POD of 0.3 is used for small numbers and 8 is used for large numbers

Note 5: Average intake and 90 percentile value

Note 6: Not genotoxic, but there is no threshold for its toxicity

COC: Scientific committee (England) for carcinogenicity of chemical substances in food, consumer commodities, and environment

ANSES: French Agency for Food, Environmental and Occupational Health & Safety (L'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail)

EFSA: European Food Safety Authority

FSA: Food Standards Agency

JECFA: Joint FAO/WHO Expert Committee on Food Additives

RIVM: National Institute for Public Health and the Environment

CFS: Hong Kong Centre for Food Safety

Spain: Catalan Food Safety Agency

BMDL: Benchmark dose limit 95% lower confidence limit $BMDL_{10}$ is BMDL for which cancer development increases by 10%.

NOAEL: Quantity for no effect, maximum dose for which no negative effect is observed

prioritize, cancer that develops in later ages or the lifelong effect on intelligence? Response to risk requires one to consider how to best distribute limited resources, including tradeoffs.

Finally, after the Great East Japan earthquake, I have had many opportunities to talk about carcinogens in food in front of individuals involved in nuclear power, and had the impression that they were not as aware of carcinogens in food as I expected. Nuclear power is a huge industry, and one can live entirely within this large bubble. If there had been measures in regard to natural carcinogens in food, on which there has been little research, by the wealth generated by nuclear power, the response after the earthquake would also have been different. Even very small effects of nuclear radiation are studied with huge funds in the nuclear community, but little is understood in regard to why substances known to be carcinogenic, such as inorganic arsenic, cause cancer in humans but not in animals. There is often no person who is clearly responsible for natural substances, and there is, therefore, no pressure in the form of attacking someone's responsibility. However, the improvement in human health and welfare is desired by all members of society, and thus, I would like as many people as possible to expand their views and think about the most pressing issues of all.

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