Quantification of Human Health Risks in Risk Assessment and Management -Framework and Applications-

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Abstract

The issues regarding risk trade-off between chemical substances with different types of toxicity have been difficult to deal with because the risks are evaluated independently and therefore cannot be compared with each other. We are proposing a new framework of quantifying human health risks, in which we use LLE (loss of life expectancy) as a measure of risks. Using life table analysis, the increase in death rate due to any kind of adverse health effect can be translated into LLE. The individual variability is explicitly included in the risk evaluation in the framework. Two applications of the framework are also described.

1. Introduction

In order to establish a reasonable risk management strategy for regulating chemical substances, the risk assessment process is essential. In the case of carcinogenic chemicals, the cancer risk level is usually quantified as the additional probability of developing cancer due to lifetime exposure to a certain carcinogenic substance. On the other hand, the case of noncarcinogenic chemicals, the method commonly used for assessing human health risks has been to derive the ratio of estimated exposure levels to a substance to its ADI (acceptable daily

intake). If the ratio exceeds one, the exposure level is regarded as "not acceptable". Although the ratio is estimated quantitatively, the judgement is qualitative, i.e., acceptable or not. Furthermore, the significance of the ratio is unclear from the viewpoint of the risk levels, particularly when the ratio exceeds one or is almost one. Since the noncancer risks are represented in a qualitative manner, it is difficult to compare a noncancer risk with cancer risks or even other noncancer risks. Therefore, the applications of the risk/benefit analysis have been so far limited to the carcinogenic substances.

In order to deal with the risk trade-off between chemical substances, a measure that can quantitatively represent the magnitude of the risks, irrespective of the type of risk, should be developed. In this paper, the proposed framework for the quantification of human health risks and two example applications are described.

2. Framework of Assessment of Human Health Risks

In the framework, individual variability was taken into account and LLE (loss of life expectancy) was used as the measure of risk (Gamo *et al.* 1995). The schematic diagram of the framework is shown in Fig. 1, in which the risk is calculated as the summation of risks to the entire exposed population. Compared with the estimations for the average case or for the worst case, the risk estimated in the proposed framework is considered a reasonable value of the risk for the exposed population as a whole. The key issues are the determination of the individual variability in the body burden of the substance and the derivation of the body burden-effect (LLE) relationship.

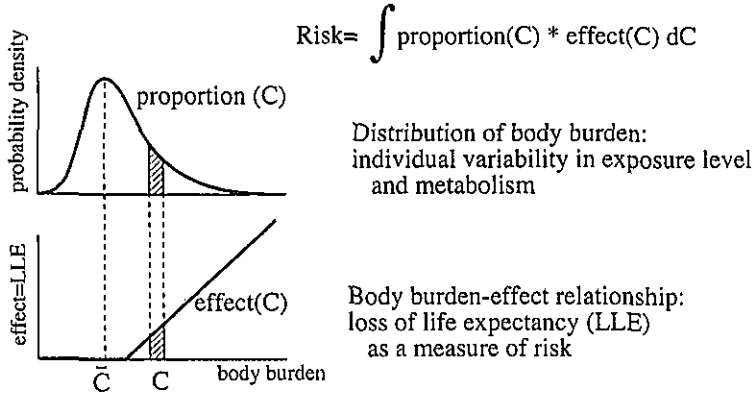

Fig. 1. Schematic diagram of the risk evaluation method.

2.1 *Individual variability*

The individual variability in body burden, shown in Fig.1, consists of variability in the exposure level and that in the metabolic rate in individual bodies. The variability in the exposure level largely depends on the exposure scenario. It is considered small if the pollutant is spread widely and the relationship between the origin of the pollutant and the

exposure is indirect. On the other hand, the variability would be large if exposure occurs near the origin of the pollutant. Although it is important to determine the variability in exposure level, little research has been conducted in Japan. The US EPA has published a compilation of the parameters related to exposure to chemical substances (US EPA 1997), in which it explicitly deals with the variability in exposure levels. According to the compilation made by Hattis *et al.* (1999), observed GSD (geometric standard deviation) values ranged from 1.3 to 5.0.

As for the variability of the metabolic rate, a GSD of 1.4 - 1.8 would be appropriate. These values are based on a report on the variability of metabolic rates in cases of generic pharmaceuticals (Masuyama 1977) and a discussion on the safety factors in risk assessment (Dourson *et al.* 1996). A GSD of 1.4 - 1.8 means that a 10-fold safety factor accounts for 99.9% - 96% of the total range of individual variability.

The variability in susceptibility to a substance can also be taken into consideration although there is no general recommendation for the value of the variability in susceptibility. For some types of toxicants, it is considered that there is no variability in susceptibility. In this case, the significance of the toxic effects is directly related to the body burden (or the toxicant concentration at the target organ). However, for other types of toxicant, there may be a large variability in susceptibility. A list of observed values of individual variability in susceptibility was also provided by Hattis *et al.* (1999).

2.2 *Loss of life expectancy*

We propose LLE as a measure of human health risks. Given the death rate by age, the life expectancy of a population can be calculated by life table analysis. LLE is calculated as the decrease in the life expectancy brought about by the increase in death rate due to adverse health effects. In other words, the adverse health effects that increase the death rate can be taken into account in the risk assessment by using LLE as a measure of human health risks.

1) *Increase in death rate due to noncarcinogenic chemicals*

When the individual variability of the body burden is considered, the population included in the upper end of the distribution histogram may have body burden higher than the threshold level. Although the adverse health effects of concern in the context of the environmental risk assessment may not be so severe, even nondeath effects would bring about an increase in death rate, resulting in a decrease in health status. Some epidemiological studies have related the decrease in health status to the increase in death rate. If possible, it is preferable to use data that are specific to the adverse health effects of concern. However, in most cases, only a generic relationship between health status and death rate is available. In such cases, the decrease in health status due to adverse health effects should be supposed based on expert judgement or estimated based on responses to questionnaires.

2) *Increase in the death rate due to carcinogenic chemicals*

As mentioned above, cancer risk is usually represented as the additional probability of developing cancer due to lifetime exposure. The probability of developing cancer can be translated into an increase in cancer death rate if the relationship between exposure to a cancer-causing agent and age when cancer death occurs is determined. LLE can be calculated using the increase in death rate due to additional occurrences of cancer. We estimated LLE corresponding to a lifetime cancer risk of 10^{-5} to be 66 minutes based on the assumptions derived from the study on radiation-induced cancer (Gamo *et al.* 1996).

3. Applications

3.1 *Prohibition of chlordane use as a termiticide*

Chlordane had long been used as a termiticide in Japan, until its use and trade were prohibited in 1986 under the Law Concerning the Examination and Regulation of Manufacture, etc. of Chemical Substances. Chlordane was banned because of its accumulation in fish over time and carcinogenicity. Chlorpyrifos, which is an organophosphorus termiticide, was one of the major alternatives to chlordane. The purpose of this case study is to estimate and compare the risk due to chlordane and that due to chlorpyrifos following the proposed framework. The details of the assessment are shown in the report by Gamo *et al.* (1995).

1) *Exposure levels to termiticides*

Three exposed populations were considered: residents of termiticide-treated houses, residents of untreated houses, and termite control workers. Because chlordane has a high potential of being accumulated in fish, consumption of fish was one of the main exposure routes, particularly for residents of untreated houses, when chlordane was used as a termiticide in Japan. Since it is considered that chlorpyrifos for termite control may not be accumulated in foods, residents of untreated houses are not exposed to chlorpyrifos. For residents of treated houses, the main exposure route is via indoor air contaminated with evaporated termiticides. For termite control workers, the exposure routes are via air at the workplace and adhesion of termiticides to the skin during their work. The estimated amounts of exposure to termiticides are summarized in Table 1.

2) *Hazards of termiticides*

The risk due to exposure to chlordane is regarded as cancer risk. The additional probability of developing cancer is calculated by multiplying the estimated exposure level by the cancer potency, for which the value of 1.3 per mg/kg/day (US EPA 1996) was applied.

Chlorpyrifos exhibits neurotoxicity, whose mode of action is inhibition of cholinesterase activity. The exposure to chlorpyrifos was translated into the internal concentration of TCP (3,5,6-trichloro-2-pyridinol, one of the metabolites of chlorpyrifos). Then, the internal concentration of TCP was related to the extent of inhibition of cholinesterase activity (Eq. 1),

which, in turn, was related to the decrease in health status represented as a CMI (Cornell Medical Index) score (Eq. 2). CMI is a questionnaire on the health status; a low CMI score indicates a poor health status. Equation 2 was developed based on the result of an interview with a medical doctor who had much experience with poisoning due to organophosphorus compounds. Then CMI score was related to the increase in the death rate (Eq. 3).

$$V/V_0 = 1/(1+0.027*C_{TCP}^{1.06})*100 \quad (1)$$

V/V_0: ratio (%) of the remaining cholinesterase activity

C_{TCP}: internal concentration of TCP (a metabolite of chlorpyrifos)

$$\text{CMI score} = -1.43*V/V_0+71.6 \qquad (V/V_0 > 50\%: \text{CMI score} = 0) \quad (2)$$

$$\lambda(x) = \exp(0.013*\text{CMI score})*\lambda_0(x) \quad (3)$$

$\lambda(x)$: death rate at age x of the population exposed to chlorpyrifos

$\lambda_0(x)$: death rate at age x of the control population

3) *Individual variability in internal concentration of termiticide*

Here, it is assumed that the individual variability follows the lognormal distribution. In order to estimate the individual variability in the internal concentration of termiticide (GSD_i), two types of variability were taken into account: variability in exposure levels (GSD_e) and that in the metabolic rate (GSD_m). GSD_m was assumed to be 1.4 for all exposed poulations. GSD_e was determined to be 3.8 for exposure via contaminated indoor air, 2.2 for exposure via consumption of fish, and 2.9 for exposure at working place. GSD_i was derived by combining GSD_e with GSD_m.

4) *Result and discussion*

Following the framework for evaluating the human health risk, LLE was calculated. Table 1 summarizes the estimation of the risk evaluation. Considering that LLE due to cancer risk of 10^{-5}, which is regarded as *de minimis* risk in the regulation of the environmental pollutants, is 66 minutes, the use of termiticide can cause risks much higher than the acceptable level. Furthermore, the replacement of chlordane with chlorpyrifos did not reduce the risk reduction for residents of treated houses and for termite control workers. However, the risk for residents of untreated houses, who receive no benefit of termite control at all, was eliminated. In this regard, the prohibition of chlordane was effective. According to the results of the risk/benefit analysis, the cost per life-year saved due to the prohibition of chlordane was estimated to be 45 million yen (Oka *et al.* 1997).

Table 1. Summary of the assessment of risk due to termiticides

	chlordane			chlorpyrifos		
	untreated houses	treated houses	workers	untreated houses	treated houses	workers
average exposure level (μg/kg/day)	0.0138	0.133	0.86	0	0.253	3.52
internal concentration (μg/kg)	0.418	4.03	26.1	0	0.234	3.25
GSD_i	2.2	4.0	3.0	2.2	4.0	3.0
LLE (days)	0.10	1.9	4.4	0	2.8	31

3.2 *Prohibition of the mercury electrode process in caustic soda production*

Since the mid-1960s, the Japanese government had introduced a succession of strict measures to reduce the environmental toxic effects of mercury, following the occurrence of two outbreaks of Minamata Disease (MD). In Japan, 95 % of caustic soda was produced using the mercury electrode process until it was completely replaced with a nonmercury process in September 1986. The reason for the replacement is that the effluent from caustic soda production using the mercury electrode process was suspected to be the cause of the possible occurrences of the third and fourth outbreaks of MD. The purpose of this case study is to estimate the risk reduction by the replacement of the mercury electrode process and to conduct the risk/benefit analysis on the efficiency of the replacement. The details of the assessment are found in the report of Nakanishi *et al.* (1998).

1) *Intake of methyl mercury*

In the Tokuyama Bay area, there were two caustic soda production plants using the mercury electrode process. The plants in the area produced one-tenth of the total caustic soda in Japan and the occurrence of the fourth outbreak of MD was suspected in the area. Therefore, the concentration of methylmercury in fish was estimated based on the condition in Tokuyama Bay. Three exposed populations were considered. Group 1: heavy fish eaters such as fishermen, who were assumed to eat only fish caught in the bay. Group 2: residents who eat only fish caught in the bay. Group 3: residents who do not eat any fish caught in the bay. Table 2 summarizes the consumption of fish caught in the bay and the levels of methylmercury intake. The individual variability in the consumption of fish was assumed to follow the lognormal distribution with a GSD of 1.5.

2) *Probability of poisoning and increase in death rate*

The relationship between the daily intake of methylmercury and the probability of paresthesia was reported by Nordberg and Strangert (1976), in which the variability in the susceptibility to methylmercury and that in the half-life of methylmercury in the body were included. The occurrence of paresthesia was related to the increase in death rate, according to the epidemiological study of MD patients (Kinjo *et al.* 1991), in which SMR (standard mortality ratio) values of 1.27 for male and 1.20 for female MD patients were reported.

3) *Result and discussion*

The results of risk estimation are summarized in Table 2, in which paresthesia risk and LLE are shown as the sums for the entire exposed population. LLE of 75.2 years was estimated as the total LLE due to exposure to methylmercury originating from caustic soda production using the mercury electrode process. According to the results of the risk/benefit analysis, the cost per life-year saved due to the prohibition of the mercury electrode process was estimated to be 570 million yen.

Table 2. Summary of the assessment of the risk due to caustic soda production using the mercury electrode process.

	group 1	group 2	group 3
population (in thousands)	3	1330	
consumption of fish caught in the bay (g/day)	320	97	0
background methylmercury intake (μg/day)	32	9.7	9.7
increment of methylmercury intake (μg/day)	8.7	2	0
paresthesia risk (case/year)	1.92	38.7	
LLE (life-years)	3.6	71.6	

4. Discussions

The framework proposed here can be applicable to any human health risk issue if the adverse effects of concern can be quantified as an increase in death rate. One of the beneficial applications other than those described in this paper is the evaluation of risk trade-off issues regarding the disinfection of drinking water, in which the risk due to infectious microbes in drinking water should be compared with the health risks due to disinfectant by-products. The use of LLE as a measure of risk is becoming popular in the generic risk analyses of various issues, including medical and safety issues. For example, Tengs *et al.* (1995) reported the values of the cost effectiveness of five hundred life-saving interventions, which were represented in terms of cost per life-year saved.

One important issue that remains beyond the scope of the proposed framework is how to deal with the adverse effects that will not increase the death rate but will decrease the quality of life. Although QALY (quality-adjusted life years) is becoming popular as a measure of risk, much care is required in its use. One reason is that the rating of the quality of life is largely subjective, and another is the ethical reason that the value of a life with low quality should not be regarded as lower than that of a life with usual quality. In order to use QALY as a complementary measure of risk with LLE, it is important to make it clear that QALY is applied to the evaluation of the risk for a population as a whole, not for a certain individual. The rating of the quality of life is usually obtained by means of questionnaires. For example, the quality of life is graded in levels ranging from death (= 0) to complete health (= 1). Alternatively, it can be measured in terms of the WTP (willingness-to-pay) for avoiding

reductions in the quality of life. Whichever approach we take, the usefulness of QALY as a measure of risk largely depends on the design of the study for rating the reduction in the quality of life.

For some chemicals such as endocrine disrupters and dioxins, adverse effects to the fetus and/or nursling are considered to be one of the most sensitive endpoints. Conversely, the risk to the fetus and/or nursling can be obvious even when the risk to the parents (adults) is negligible. In fact, the TDI (tolerable daily intake) of dioxins in Japan was determined so that exposure at the TDI level would not pose adverse effects to the fetus. Had the TDI level been determined based on the adverse health effects to the parents (adults), the value might have been much higher. The adverse effects to the fetus and/or nursling give rise to two types of risk. One is the risk to the parents (adults) and the other is the risk to the fetus and/or nursling. If the health effects to the parents are negligible, the risk to the parents is evaluated as the reduction in the quality of life due to infertility or children affected by some disorders. On the other hand, in order to deal with the risk to the fetus and/or nursling, we should explicitly face the problem of intergenerational equity. The equity in risk distribution, both intergenerational and intragenerational, is one of the most important issues in risk management. The development of a consensus on how to deal with the issues of equity in risk distribution is strongly desired.

The two topics, "the individual variability (and uncertainty) in exposure levels and susceptibility to environmental pollutants" and "LLE (and QALY) as a common measure of risk", have become increasingly predominant at scientific meetings on risk assessment. However, they have been discussed separately so far. The framework proposed here is considered state-of-the-art and promising for the assessment of human health risk.

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