Ranking Risks of Chemical Substances in Japan

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Abstract

The general framework developed for assessing chemical risks was applied to twelve chemical substances, namely, radon, formaldehyde, dioxins, cadmium, toluene, chlorpyrirofs, arsenic, benzene, mercury, xylene, DDT, and chlordane. In the framework, loss of life expectancy (LLE) was adopted as a measure of risks and individual variabilities in exposure, metabolism, and sensitivity were taken into account. The risk levels of the chemical substances were estimated to range from LLE of 0.01 to 10 days.

1. Introduction

In our daily life, we are exposed to various chemical substances, some of which are suspected to pose significant health risk. Quantitative evaluation of risks is considered important for rational management of chemical substances, for example, the priority setting or risk-benefit analysis of the risk reduction.

The methodology for risk assessment of carcinogenic chemicals has been different from that of non-carcinogenic chemical substances. Cancer risks from carcinogenic chemicals are usually evaluated in terms of the lifetime probability of occurrence of cancer due to lifetime exposure, e.g. 10⁻⁵. Although there exist caveats on the use of cancer potency (slope factor) because of the uncertainties in the derivation, the lifetime cancer risk as a common measure has enabled quantitative risk assessment and management of risks from carcinogenic chemicals. On the other hand, the non-cancer risks from non-carcinogenic chemicals have been evaluated
in terms of Hazard Quotient (the ratio of exposure to safe dose level) or Margin of Exposure (the ratio of safe dose level to exposure). Even though such indices may be helpful for judging whether the exposure level would not pose significant health risk, we cannot tell the risk levels, in particular, when the exposure level is near or a little larger than safe dose level.

The general framework developed for assessing chemical risks (Gamo et al. 1995) was applied to twelve chemical substances. In this presentation, we show the overview of the framework and the results obtained for the twelve chemicals. Table 1 shows the chemical substances whose risk levels were evaluated. Half of them come from air while others come from food. Approximately half of them are regarded as carcinogenic. The risk levels were estimated for the current situation of the general population in Japan unless otherwise stated. The estimation of each chemical substance was concisely summarized as a risk-estimation sheet that is attached in the end of this paper.

### Table 1. The substances evaluated in this study

<table>
<thead>
<tr>
<th></th>
<th>inhalation</th>
<th>ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>carcinogens</td>
<td>benzene</td>
<td>arsenic</td>
</tr>
<tr>
<td></td>
<td>formaldehyde</td>
<td>chlordane</td>
</tr>
<tr>
<td></td>
<td>radon</td>
<td>DDTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dioxins</td>
</tr>
<tr>
<td>non-carcinogens</td>
<td>chlorpyrifos</td>
<td>cadmium</td>
</tr>
<tr>
<td></td>
<td>toluene</td>
<td>mercury</td>
</tr>
<tr>
<td></td>
<td>xylene</td>
<td></td>
</tr>
</tbody>
</table>

2. **General Framework**

The flowchart of risk evaluation is shown in Figure 1. The risks are estimated in terms of LLE (Loss of Life Expectancy), which is derived from life table analysis based on the increase in mortality rate. Health effects, both cancer and non-cancer effects, are related to increase in mortality rate. The actual procedure for estimation depends on data availability. For example, the linkage would be shortcut in some cases, that is, an epidemiological study would show the direct relationship between exposure and increase in mortality rate.

![Fig. 1. Flowchart of risk estimation](image)

**2.1 Loss of Life Expectancy (LLE)**

Figure 2 shows the schematic diagram of loss of life. Under the adverse health effects
due to exposure to chemical substances, the survival curve would be shifted downward. LLE is estimated as the total loss of life for the population divided by the initial population, in other words, the expected loss of life at age 0.

![Fig. 2. Schematic diagram of loss of life](image)

**In the case where substance-specific information on increase in mortality or resulting LLE is not available, general information is applied.** For example, the morbidity is related to the general decrease in health status and then increase in mortality rate (Fig. 3). Table 2 shows the default values of LLEs corresponding to the severity of health effects. The values were derived based on the epidemiological study that relates the generic health status with increase in mortality rate. The general assumption for cancer risk is that the lifetime cancer risk of $10^{-5}$ corresponds to LLE of 1 hour (Gamō et al. 1996).

![Fig. 3. Schematic diagram estimating increase in mortality rate.](image)

**Table 2. Default table for LLE due to adverse health effects.**

<table>
<thead>
<tr>
<th>Health status category</th>
<th>LLE (years) *1</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>impairment (unable to conduct daily life)</td>
</tr>
<tr>
<td>II</td>
<td>impairment (difficult in daily life)</td>
</tr>
<tr>
<td>III</td>
<td>chronic illness (more than 2 of illness *2)</td>
</tr>
<tr>
<td>IV</td>
<td>chronic illness (one of illness *2)</td>
</tr>
<tr>
<td>V</td>
<td>symptoms (one of convulsion, fatigue, etc.)</td>
</tr>
<tr>
<td>VI</td>
<td>no symptoms</td>
</tr>
</tbody>
</table>

*1 hypertension, asthma, epilepsy, diabetes, cancer, tuberculosis, gastric ulcer, hepatopathy, etc.

*2 based on the mortality rates reported Berkman and Breslow (1983)

**2.2 Individual Variability**

Risks are estimated as population risks. For deriving population risk, considering individual variability is essential (Fig. 4). Individual variabilities in exposure, metabolism,
and sensitivity were taken into account. Default assumption is that variabilities follow log-normal distribution. <Non-cancer Risk> The proportion of people that suffer from a specific health effect is calculated based on the distribution of individual variability and the threshold of the effect. <Cancer Risk> Since the distribution of individual variability is skewed, the lifetime cancer risk for the total population would be evaluated higher than that based on the average exposure level. Table 3 shows the default values for individual variabilities that were used in this study. If available, the substance-specific data should be prioritized for use.

![Probability graph showing individual variability in risk estimation](image)

**Table 3. Default values for individual variabilities**

<table>
<thead>
<tr>
<th>Geometric Standard Deviation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>metabolism</td>
<td>1.4 (based on the metabolizing rate of chemicals: Masuyama 1977)</td>
</tr>
<tr>
<td>exposure via fish</td>
<td>2.2 (based on body burden of PCB: Masuyama 1977)</td>
</tr>
<tr>
<td>sensitivity</td>
<td>2.7 (based on toxicity of methylmercury poisoning: Nordberg 1976)</td>
</tr>
</tbody>
</table>

3. Ranking Risks of 12 chemical substance

The risk levels of the assessed 12 chemical substances ranged from LLE of 0.01 to 10 days (Fig.5). It was estimated that risk level was the highest for Radon and the lowest for organochlorine pesticides, DDT and chlordane. Considering that the lifetime cancer risk of $10^{-5}$ corresponds to LLE of 1 hour (=0.04 day), the risk levels of the chemical substances evaluated here seem higher than so-called de minimis risk level ($10^{-5}$). We still have many substances to be assessed, for example, particulate matters, PAHs, chloroform, ethylbenzene, lead, 1,3-butadiene, trihalomethane, etc.

The advantage of the framework applied here is its flexibility. It can be applied to both carcinogenic and non-carcinogenic substances. If there are enough data, it works as a mechanistically-based framework. Here, the procedures of risk estimation for cadmium, mercury, and chlorpyrifos belong to this type of assessment. On the other hand, if only the
NOEL value and suspected health effects are known, like toluene and xylenes, the procedure should be simplified. In such a case, the framework can be regarded as a variation of MOE (margin of exposure) concept. While MOE represents the distance from exposure level to the safe level, the framework in this study standardizes the MOE with the magnitude of individual variability and then weights it with the severity of suspected health effect.

It is essential to keep revising the default values applied to the framework. As for individual variabilities, discussion on the current safety factors and compilation of the exposure factors for Japanese are helpful. As for LLE, we need to improve the method that relates the suspected health effects to the reduction of health status and resulting LLE. Such indices as QALY (Quality Adjusted Life Years) or DALY (Disability Adjusted Life Years) are also attractive for evaluating the health effects or the reduction of health status.

![Risk Levels of Chemical Substances](image)

Fig. 5. Estimated risk levels of 12 chemical substances

4. References
**Dioxins**

**Exposure**  
**Inhalation**

1.67 pgTEQ/kg/day  
the arithmetic mean of the values of seven areas, which was obtained from total diet study held in 1997 and 1998. This value includes dioxins, fulans and co-PCBs.

**Lifetime Cancer Risk**  
According to the EPA’s external draft in 1997, the slope factor of TCDD is 1.0 E-4 per pg/kg/day. The lifetime cancer risk corresponds to the median exposure level is calculated as:

\[
1.67 \text{ (pgTEQ/kg/day)} \times 1.0 \text{ E-4 (per pgTEQ/kg/day)} = 1.67 \text{ E-4}
\]

**LLE**  
9.9 days

**Increase in Lung Cancer**  
Relative risk of lung cancer due to exposure to radon of 15.5 Bq/m³ was estimated based on BEIR (Biological Effects of Ionizing Radiation) VI report.

<table>
<thead>
<tr>
<th>relative risk</th>
<th>male</th>
<th>female</th>
</tr>
</thead>
<tbody>
<tr>
<td>smoker</td>
<td>1.042</td>
<td>1.046</td>
</tr>
<tr>
<td>non-smoker</td>
<td>1.100</td>
<td>1.106</td>
</tr>
</tbody>
</table>

% of smokers: male=72 %, female=15%  
(Ministry of Health and Welfare 1998)

**Mortality**  
Lethality of lung cancer was assumed to be 1.

\[
M(x) = M_0(x) + DLC(x)
\]

\[
M(x) \text{, } M_0(x): \text{mortality at age x of exposed and control population}
\]
\[
DLC(x): \text{increment of lung cancer at age x}
\]

**LLE**  
9.9 days

**Exposure**  
**Inhalation**

15.5 Bq/m³  
the arithmetic mean of the concentration in indoor air in 900 houses in nationwide survey (Sanada et al. 1999)

**Radon**

**Formaldehyde**

65 ug/m³  
the arithmetic mean of personal exposure level, which was obtained from the nationwide survey on indoor air pollutants.

**Lifetime Cancer Risk**  
For inhalation exposure to formaldehyde, the EPA IRIS database provides the slope factor of 1.3 E-5 per ug/m³.

\[
65 \text{ (ug/m³)} \times 1.3 \text{ E-5 (per ug/m³)} = 8.5 \text{ E-4}
\]

**LLE**  
One hour LLE per lifetime cancer risk of 10⁻⁵  
3.5 days

**Exposure**  
**Inhalation**

25.5 ug/day  
the geometric mean of 588 subjects (Watanabe 2000)

**Formaldehyde**

**Body Burden**  
Chronic Exposure

\[
50 \text{ ug/day} = 2.5 \text{ ug/g creatinine} = \text{Concentration in renal cortex}
\]

50 ug/g  
according to reports from Sweden (1998) and US (1999)

**Biomarker & Morbidity**  
It is reported that b₂-microglobulin (protein of low molecular weight) excretion in urine of >1000 ug/g creatinine causes increase in mortality. The dose-response curve was derived based on that reported by Sweden (1998) for >200-600 ug/g cre.

For individual variability for exposure and metabolism GSD of 2, which is based on that in urinary excretion of Cd, were applied. 0.054 % of population was estimated to suffer from b₂m >1000 ug/g cre..

**Mortality Rate**  
Relative risk of lung cancer due to exposure to radon of 15.5 Bq/m³ was estimated based on BEIR (Biological Effects of Ionizing Radiation) VI report.

**Exposure**  
**Food**

25.5 ug/day  
the geometric mean of 588 subjects (Watanabe 2000)

**Cadmium**

**Exposure**  
**Food**

25.5 ug/day  
the geometric mean of 588 subjects (Watanabe 2000)

**Mortality**

% of smokers: male=72 %, female=15%  
(Ministry of Health and Welfare 1998)

**LLE**  
0.87 days

**For inhalation exposure to formaldehyde, the EPA IRIS database provides the slope factor of 1.3 E-5 per ug/m³.**

\[
65 \text{ (ug/m³)} \times 1.3 \text{ E-5 (per ug/m³)} = 8.5 \text{ E-4}
\]

**One hour LLE per lifetime cancer risk of 10⁻⁵**

\[
3.5 \text{ days}
\]

**For inhalation exposure to formaldehyde, the EPA IRIS database provides the slope factor of 1.3 E-5 per ug/m³.**

\[
65 \text{ (ug/m³)} \times 1.3 \text{ E-5 (per ug/m³)} = 8.5 \text{ E-4}
\]

**One hour LLE per lifetime cancer risk of 10⁻⁵**

\[
3.5 \text{ days}
\]
### Toluene

**Exposure**  
Inhalation  
34.2 ug/m³  
The median of 385 personal exposure levels, which was obtained from the nationwide survey in 1998.

**Morbidity**  
LOAEL of neurological effects in occupational exposure was 79 mg/m³, which was used as the basis of criteria in the EPA IRIS database and air quality guideline 2000 of WHO. It was assumed that the most sensitive person in the subject population had the average sensitivity in the general population. A factor of 10 was applied for extrapolating LOAEL to NOAEL. Then, the threshold was assumed to be 7900 ug/m³. Based on the result of survey, the individual variability (GSD) for exposure level was derived to be 4.6. The GSDs for metabolism and sensitivity were assumed to be 1.4 and 2.7, respectively, which are the default values of this assessment. The proportion which exceeded the threshold was estimated to be 0.17%.

**Mortality**  
It was assumed that exposure exceeding the threshold causes subtle health effects which are categorized in category V (LLE of 1.05 years) in the default table.

**LLE**  
0.63 days

### Chlorpyrifos

**Exposure**  
Inhalation  
0.15 ug/m³  
Based on the indoor concentration in the house with termite control (Nagami 1991 and Yoshida 1994).

**Body Burden**  
The internal concentration of TCP (3,5,9-trichloro-2-pyridinol) were estimated by a one-compartment model.

**Biomarker**  
The mode of action of chlorpyrifos is inhibition of cholinesterase (ChE). The relationship between ChE inhibition and internal TCP concentration was derived based on the study on termitecidic applicators.

**Morbidity**  
ChE activity  
poisoning  
<50% of control  mild to moderate  
< 20% of control  severe  
The GSDs for exposure: 3.8, metabolism: 1.4, and sensitivity: 2.7. The proportion suffering mild to moderate (severe) poisoning was estimated to be 0.031 (0.0014) %.

**Mortality**  
poisoning  
category  
III, IV, and V  2.11  
I and II  10.3  

**LLE**  
0.29 days

### Arsenic (inorganic)

**Exposure**  
Food  
0.22 ug/kg/day  
Toyoda (1998) reported that the intake of total arsenic was 170-230 ug/day. Here, average intake was regarded as 200 ug/day. The percentage of inorganic arsenic of 6.8% (Mohri 1990) was used to estimate the intake of inorganic arsenic. Body weight of 60 kg was assumed.

**Lifetime Cancer Risk**  
According to the EPA IRIS database, the slope factor for arsenic is 1.5 per mg/kg/day. The lifetime cancer risk corresponding to the average exposure level is calculated as;  
0.22 (ug/kg/day) * 1.5 (per ug/kg/day) = 3.3 E-4

**LLE**  
For individual variability of exposure levels, the default value of GSD = 2.2 was applied. Inorganic arsenic causes skin cancer, whose lethality is considered low. Based on the statistics in Japan, the lethality of skin cancer was supposed to be 14%. One hour per lifetime cancer risk of 10⁻⁷.

**LLE**  
0.23 days

### Benzene

**Exposure**  
Air  
3.3 ug/m³  
The median of 385 personal exposure levels, which obtained from the nationwide survey in 1998.

**Lifetime Cancer Risk**  
According to the EPA IRIS database, the slope factor for benzene is 2.2-7.8 E-6 per ug/m³. Here, the average value of the range, 5 E-6 per ug/m³, was used. The lifetime cancer risk corresponding to the exposure level is calculated as;  
3.3 (ug/m³) * 5 E-6 (per ug/m³) = 3.3 E-5

**LLE**  
Based on the result of survey, the individual variability (GSD) of exposure level was derived to be 3.37. One hour per lifetime cancer risk of 10⁻⁷.

**LLE**  
0.14 days
### Mercury

**Exposure**
- Food: 15 ug/day
  - based on the result of total diet study (Toyoda 1998).

**Body Burden**
- Using a one-compartment model, the following relationship between intake and body burden was derived:
  \[ \text{Body burden (mg)} = 98 \times \text{Daily intake (mg/day)} \]

**Morbidity**
- The relationship between body burden and severity of poisoning was derived based on the dose-response reported by Al-Shahristani (1976).
- Individual variability (GSD) including both exposure and metabolism was supposed to be 1.7 based on the GSD of mercury concentration in hair (Masyuyama 1976).
- GSD for sensitivity was assumed to be 2.73, which was used by Nordberg (1976).
- The proportion suffering from mild (moderate, severe) poisoning was estimated to be 1.1E-4 (2.9E-5, 1.1E-6).

**Mortality**
- Poisoning category: IV and V = 1.53, III and II = 4.76, I = 14.3
- LLE = 0.12 days

### Xylenes

**Exposure**
- Inhalation: 14.9 ug/m³
  - the median of 385 personal exposure levels, which obtained from the nationwide survey in 1998.

**Morbidity**
- NOAEL for adverse effects on CNS was estimated to be 300 mg/m³ as the result of 4 hours exposure of human volunteers to xylenes (IPCS1997).
- The concentration was converted to daily average exposure: 300 (mg/m³) * (4/24) = 50 (mg/m³).
- It was assumed that the most sensitive person in the volunteers had the average sensitivity in the general population. An factor of 10 was applied for extrapolating from short term to chronic exposure. Then the threshold level of 5000 ug/m³ was estimated.
- Based on the result of survey, the individual variability (GSD) for exposure level was derived to be 3.5. GSDs for metabolism and sensitivity were assumed to be 1.4 and 2.73, which are the default values of this assessment.
- The proportion which exceeded the threshold was estimated to be 0.077%.

**Mortality**
- It was assumed that exposure exceeding the threshold causes subtle health effects which are categorized in category V (LLE of 1.05 years) in the default table.

### DDT & related compounds

**Exposure**
- Food:
  - p',p-DDT: 0.12 ug/day
  - p',p-DDE: 0.29 ug/day
  - p',p-DDD: 0.062 ug/day
  - based on the result of total diet study (Toyoda 1998).

**Lifetime Cancer Risk**
- According to EPA IRIS database, the slope factors for p,p-DDT, p,p-DDE, and p,p-DDD are 0.34, 0.34, and 0.24 per mg/kg/day, respectively. The lifetime cancer risk corresponding to the median exposure level was calculated to be 2.6E-6.

**LLE**
- For individual variability of exposure levels, the default value of GSD = 2.2 was applied.
- One hour per lifetime cancer risk of 10⁻⁵
  - 0.015 days

### Chlordane

**Exposure**
- Food: 0.24 ug/day
  - based on the total diet study in 1980's and the time trend of concentration in the fish taken near Japan. The value is supported by the recent total diet studies.

**Lifetime Cancer Risk**
- According to EPA IRIS database, the slope factor of chlordane is 0.35 per mg/kg/day. The lifetime cancer risk corresponding to the median exposure level was calculated to be 1.6E-6.

**LLE**
- For individual variability of exposure levels, the default value of GSD = 2.2 was applied.
- One hour per lifetime cancer risk of 10⁻⁵
  - 0.009 days