Title: Ranking the Risks of Twelve Major Environmental Pollutants That Occur in Japan

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Abstract:

The risks posed by twelve major environmental pollutants in Japan were evaluated and ranked on the same scale. The substances included arsenic, benzene, cadmium, chlordane, chlorpyrifos, DDTs, dioxins, formaldehyde, methylmercury, radon, toluene, and xylenes. Approximately half of these substances are carcinogenic while the others are non-carcinogenic. We applied a risk estimation framework that can evaluate both cancer and non-cancer risks on the same scale. The framework consists of two parts: the calculation of the probability of adverse health effects, and the evaluation of the severity of the effects. In order to calculate the probability of adverse health effects, the individual variabilities in exposure level, metabolizing rate, and sensitivity were taken into account. LLE (loss of life expectancy; days) was used as the measure of severity of the adverse health effects and of the resulting risk level. The risk level of the substances in terms of LLE ranged from approximately 0.01 to 10 days. The risks from radon and formaldehyde were found to be the highest, while the risks from DDT and chlordane were the lowest. Our findings also suggested that the risk levels posed by non-carcinogenic substances could be comparable with those posed by carcinogenic substances.

Keywords: Cancer risk, Non-cancer risk, Loss of Life Expectancy, Individual variability.

1. Introduction

In our daily lives we are exposed to various chemical substances, some of which are suspected to pose significant health risks. The quantitative evaluation of risk is considered to be essential for developing rational methods for managing environmental chemical substances. Such methods include setting priorities for risk reduction and performing risk-benefit analyses of the countermeasures.

Conventionally, the risk assessment procedures for carcinogens and non-carcinogens have been completely different from each other. The cancer risks posed by carcinogenic chemicals have been evaluated in terms of the lifetime probability of the occurrence of cancer due to lifetime exposure (USEPA, 1986). In contrast, the non-cancer risks posed by non-carcinogenic chemicals have been evaluated by comparing the level of exposure to the substance with the substance's NOAEL (No Observed Adverse Effect Level) or ADI (Acceptable Daily Intake). Even though using such a procedure for non-carcinogens may be helpful in determining whether or not a given level of exposure would pose significant health effects, the procedure does not provide any information on the magnitude of the risk. As a result, it is not possible to compare the risks of various substances with each other, nor to reasonably prioritize the countermeasures adopted for risk reduction.

The authors have developed a framework for evaluating the risks posed by chemical substances that enables us to quantitatively evaluate both cancer and non-cancer risks on the same scale (Gamo et al., 1995). In this study, we applied the framework to twelve chemical substances that are considered to pose significant risks to the general population of Japan, and we were able to rank the risks posed by these substances relative to one another.

2. Methods

2.1. Subjects

The risks posed by twelve chemical substances (Table 1) were evaluated. The substances evaluated were selected from the major environmental pollutants in Japan. Half of them are pollutants that are inhaled, while the others are ingested, and approximately half of them may be carcinogenic. The risk levels were estimated on the basis of exposure levels that currently obtain for the general population of Japan unless otherwise stated.

2.2. Generic description of the framework of risk estimation

We applied a framework that was modified from that described in our previous article (Gamo et al., 1995). Figure 1 shows a schematic diagram of the estimation of non-cancer risks as an example of the framework. The framework consists of two parts: calculating the probability of adverse health effects, and evaluating the severity of the effects.

<Calculation of the probability of adverse health effects>

For non-carcinogenic health effects, it was assumed that an individual would suffer from a toxic effect if the body burden of the substance exceeds the individual's threshold body burden. Individual variabilities in exposure level, metabolizing rate, and threshold body burden were taken into account. Lognormal distributions were assumed for the distributions of those variabilities.

Assuming that a variable r is defined as the ratio of the actual body burden to the threshold body burden, the probability for a toxic effect to occur is calculated as the probability that the variable r is greater than one. In cases where the body burden can be supposed to be

proportionally related to the exposure level and metabolizing rate, the geometric mean (GM) of *r* is considered to be equal to the ratio of the GMs of the actual exposure level and the threshold exposure level. It should be noted that the GM of the threshold exposure is not NOAEL (No Observed Adverse Effect Level) in a population, but rather ED_{50} (Effect Dose 50%). Assuming that the variabilities in the exposure level, metabolizing rate and threshold body burden are all independent of each other, the geometric standard deviation of *r* (GSD_r) is defined as

$$(\ln(GSD_r))^2 = (\ln(GSD_e))^2 + (\ln(GSD_m))^2 + (\ln(GSD_t))^2 \quad (1),$$

where GSD_e, GSD_m, and GSD_t are the GSDs for the exposure level, metabolizing rate, and threshold body burden, respectively.

The substance-specific dose-response relationship was prioritized for use when it was available. Since the dose-response relationship would already reflect the variability in both the metabolizing rate and the threshold body burden, only the variability in exposure level was combined with the dose-response relationship in order to obtain the probability of the toxic effect.

For carcinogenic chemicals, the lifetime probability of cancer was calculated by multiplying the exposure level by the cancer slope factor (USEPA, 1986). Assuming that the cancer probability would depend on the body burden of the carcinogen, we took into account the individual variabilities in exposure level and metabolizing rate. Since lognormal distributions are skewed, the arithmetic mean of cancer probability is calculated as larger than the GM value.

If the substance-specific GSD values for individual variabilities were not available, we used the default values shown in Table 2 for both non-cancer and cancer effects.

<Evaluation of the severity of the effects>

The severity of the toxic effects was evaluated in terms of LLE (loss of life expectancy), which is derived by life table analysis from the increase in mortality rate. A detailed description of how LLE is estimated in this study can be found in our]previous report (Gamo et al., 1995). If the LLE value specific to the suspected toxic effect was not available, we categorized the suspected effects according to depressed health statuses for which the LLE values were available (Table 3). For carcinogenic effects, we applied a LLE of 0.046 days to the lifetime probability of cancer of 10^{-5} based on the calculation of Gamo et al. (1996). The lethality of cancer was assumed to be one unless otherwise specified.

2.3. Summaries of risk calculations

a. arsenic (inorganic)

The cancer risk due to exposure via ingestion was evaluated. The GM of exposure to total arsenic was assumed to be 200 μg/day based on the results of the total diet study (Toyoda et al., 1998). Mohri et al. (1990) reported that approximately 6.8 % of total arsenic intake was inorganic, based on a duplicate diet study. To account for individual variability in body burden, a GSD of 2.2 (Table 2) was applied. According to the USEPA IRIS database (USEPA,1998a), the oral slope factor for skin cancer due to exposure to inorganic arsenic is 1.5 (per mg/kg/day). The lethality of skin cancer was assumed to be 15 % based on the ratio of the number of cases (Ajiki et al., 2000) to the number of deaths (Ministry of Health and Welfare, 1997a) in 1995.

b. benzene

The cancer risk due to exposure via inhalation was evaluated. Based

on the results of a nationwide survey of personal exposure levels (Ministry of Health and Welfare, 1999a), the GM of the exposure level was determined to be 3.3 μg/m^3 and the GSD was determined to be 3.4. A GSD of 1.4 (Table 2) for the variability in metabolizing rate was also taken into account. We applied the inhalation unit risk of 5 * 10^{-6} (per μg/m^3), which is the mid-value of the range of 2.2 - 7.8 * 10^{-6} (per μg/m^3) shown in the USEPA IRIS database (USEPA, 2000).

c. cadmium

The non-cancer risk due to exposure via ingestion was evaluated. Based on the exposure levels reported by Watanabe et al. (2000), Ikeda et al. (2000), and Toyoda et al. (1998), the GM of the exposure levels was assumed to be 25 μg/day. It is known that exposure to cadmium can cause renal dysfunction, for which 2-microglobulin in urine is one of the sensitive indicators. Nogawa et al. (1989) reported that microglobulinuria (urinary 2-microglobulin > 1000 μg/g creatinine) would result in increased mortality, for which the hazard ratios were 1.47 for males and 2.04 for females. The dose-response between exposure and microglobulinuria was obtained by modifying that shown in Järup et al. (1998). Based on the individual variability in urinary excretion of cadmium (Ikeda et al.,2000, and Watanabe et al., 2000), a GSD of 2 was used to represent the variability in the body burden for cadmium. The increase in mortality was translated into LLE by using life table analysis.

d. chlordane

The cancer risk due to exposure via ingestion was evaluated. Based on the exposure level in the 1980's (Gamo et al., 1995) and the time trend of chlordane concentrations in fish from 1983 to 1993 (Tani et al., 1996), the GM of the exposure level was assumed to be 0.24 μg/day. A GSD of 2.2 (Table 2) was used to represent the individual variability

in body burden. According to the USEPA IRIS database (USEPA, 1998b), the oral slope factor is 0.35 (per mg/kg/day).

e. chlorpyrifos

The non-cancer risk due to exposure via inhalation was evaluated for the residents of a house in which chlorpyrifos was used for termite control. Based on the reported indoor concentrations (Nagami et al., 1991, Yoshida, 1994, Yoshida et al., 2000, Katsura et al., 1996), 0.15 $\mu g/m^3$ was used as the GM of exposure concentration. The dose-response relationship between exposure to chlorpyrifos and inhibition of cholinesterase (ChE) activity follows that used in Gamo et al. (1995). It was assumed that ChE activity of less than 50% that observed in the controls would result in mild to moderate poisoning (categories III, IV, and V in Table 3), while ChE activity of less than 20% that observed in the controls would result in severe poisoning (categories I and II). The LLE due to mild to moderate poisonings and that due to severe poisonings were determined to be 2.11 and 10.3 years, respectively. A GSD of 3.8 was taken as the variability in the exposure level, as in Gamo et al. (1995). To account for individual variability in metabolizing rate and sensitivity, GSDs of 1.4 and 2.7 (Table 2) were used.

f. DDTs

The cancer risk due to exposure via ingestion was evaluated. Based on the results of the total diet study (Toyoda et al., 1998), the GM of the levels of exposure to DDT, DDE and DDD were assumed to be 0.12, 0.29, and 0.062 µg/day, respectively. To account for individual variability in body burden, a GSD of 2.2 (Table 2) was used. According to the USEPA IRIS database, the oral slope factors for DDT, DDE, DDD are 0.34 (USEPA 1991), 0.34 (USEPA, 1988b), and 0.24 (per mg/kg/day) (USEPA, 1988a), respectively.

g. dioxins

The cancer risk due to exposure via ingestion to PCDDs, PCDFs, and co-PCBs was evaluated. Based on the total diet study performed in 1997 (Toyoda et al., 1999), the GM of the exposure levels was assumed to be 120 pg-TEQ/day. To account for individual variability in body burden, a GSD of 2.2 (Table 2) was used. According to the US EPA's external draft in 1997 (USEPA, 1997), the slope factor for TCDD is $1 * 10^{-4}$ (per pg/kg/day).

h. formaldehyde

The cancer risk due to exposure via inhalation was evaluated. According to the results of a nationwide survey of personal exposure levels (Ministry of Health and Welfare, 1997b), the arithmetic mean of the exposure level was found to be 65 μg/m^3. A GSD of 1.4 (Table 2) was also taken into account. According to the USEPA IRIS database (USEPA, 2000), the inhalation unit risk is $1.3 * 10^{-5}$ (per μg/m^3).

i. methylmercury

The non-cancer risk due to exposure via ingestion was evaluated. Yumita et al. (1997) estimated that the typical exposure level in Japan in 1996 was approximately 15 μg/day, which we regarded as the GM of the exposure level. The level of body burden was estimated by using the one-compartment model with first-order elimination. The GSD of variability in body burden was assumed to be 1.7 on the basis of the GSD of mercury concentration in hair (Masuyama 1976). Based on the dose-response relationship reported by Al-Shahristani et al. (1976), the GMs of the threshold body burden for mild, moderate, and severe poisoning were assumed to be 89, 137, 312 (mg), respectively. Following Nordberg and Strangert (1976), a GSD of 2.7 was applied to represent

the individual variability in the threshold levels. The LLEs for mild (categories IV and V in Table 3), moderate (categories III and II), and severe (category I) were determined to be 1.53, 4.76, and 14.3 years, respectively.

j. radon

The cancer risk due to exposure via inhalation was evaluated. Sanada et al. (1999) reported 15.5 Bq/m^3 as the arithmetic mean for the indoor concentration of radon. The relative risk of lung cancer due to exposure to radon at a level of 15.5 Bq/m^3 was estimated based on the dose-response relationship shown in the BEIR (Biological effects of ionizing radiation) VI report (NRC, 1999). The smoking rate among Japanese (Ministry of Health and Welfare, 1999b) was also taken into account. The increase in lung cancer was translated into LLE by life table analysis.

k. toluene

The non-cancer risk due to exposure via inhalation was evaluated. Based on the results of a nationwide survey of personal exposure levels (Ministry of Health and Welfare, 1999a), a GM of 34.2 μg/m^3 and a GSD of 4.6 were derived for exposure to toluene. USEPA (1992) determined the LOAEL to be 119 mg/m^3 based on an occupational study. A factor of 10 was assumed for extrapolating LOAEL to NOAEL, and it was assumed that the most sensitive person in the occupational population would be of average sensitivity in the general population. In this way, 12 mg/m^3 was obtained as the GM of the threshold level. To account for individual variability in metabolizing rate and sensitivity, GSDs of 1.4 and 2.7 (Table 2), respectively, were used. The toxic effect due to exposure exceeding the threshold level was assumed to be in category V in Table 3.

l. xylenes

The non-cancer risk due to exposure via inhalation was evaluated. Based on the results of a nationwide survey of personal exposure levels (Ministry of Health and Welfare, 1999a), a GM of 14.9 μg/m^3 and a GSD of 3.5 were derived for exposure to xylenes. IPCS (1997) showed a NOAEL of 300 mg/m^3 as a result of 4 hours of exposure in human volunteers. The value was converted into a daily average concentration of 50 mg/m^3 (= 300 * (4/24)). A factor of 10 was applied for extrapolating short-term exposure to chronic exposure, and it was assumed that the most sensitive of the volunteers would have the average sensitivity of the general population. In this way, 5 mg/m^3 was obtained as the GM of the threshold level. To account for individual variability in metabolizing rate and sensitivity, GSDs of 1.4 and 2.7 (Table 2), respectively, were applied. The toxic effect due to exposure exceeding the threshold was assumed to be in category V in Table 3.

3. Results and Discussion

Figure 2 shows the risk levels of the twelve chemical substances assessed in this study. The figure also includes the risk level posed by diesel exhaust particles (DEP) as predicted by Iwai and Utiyama (2000). In their study, they estimated the risk due to DEP in terms of the probability of lung cancer. The risk levels shown in Figure 2 ranged from 0.009 to 14 days. Since the lifetime cancer risk of 10^{-5} (0.046 days in terms of LLE) is usually used as the maximum negligible risk, most of the chemical substances evaluated here are considered to pose significant risk.

It is noteworthy that the risk levels posed by organochlorine pesticides, DDT and chlordane, were the lowest among the substances

evaluated. Finding such low risk levels for organochlorine pesticides at present is probably a result of the strict regulations enforced on persistent carcinogens in the past. Although persistent carcinogens have been the most important targets in the risk assessment of environmental pollutants, the results of this study suggest that there are various pollutants whose risk levels are far higher than the risk currently posed by organochlorine pesticides. The results also suggest that the risk levels posed by non-carcinogenic pollutants are comparable with those posed by carcinogenic pollutants. It therefore becomes increasingly important to evaluate both cancer and non-cancer risks.

The framework applied here is flexible and can be adjusted depending on data availability. The framework is mechanistically based when a large amount of data is available. This mechanistically based type of assessment was used in the present study in the procedures for cadmium, methylmercury, and chlorpyrifos. However, if only the NOAEL value and the suspected health effects are known, as in the cases of toluene and xylenes, a simplified procedure is applied. The simplified framework can be regarded as a variation of MOE (margin of exposure) analysis. Here, the MOE value, which is the ratio of NOAEL to the exposure level, was standardized by using the magnitude of individual variability in order to obtain the probability of the suspected health effects. It was then weighted by the value of LLE which represents the severity of the effect.

One negative aspect of the flexibility of the framework is that the estimated risk levels may involve various levels of uncertainty. Even if the risk estimation conducted for each substance is state-of-the-art, the difference in data availability from substance to substance would result in a difference in the uncertainty of the risk estimation. In order to compensate for the difference in uncertainty, we can use the 95% confidence limit, for example, of the estimated risk for developing

the risk ranking. In the calculation of the 95% confidence limit, the uncertainties are included in the risk estimation, and then a higher uncertainty would result in a higher risk level. However, since the magnitude of uncertainty is difficult to quantify in most cases, a ranking based on the 95 % confidence limit of the estimated risks also suffers from significant uncertainty.

In this study, the default values shown in Tables 2 and 3 were applied when the substance-specific data were not available. Although they should be replaced with substance-specific data in the detailed risk estimation of each substance, the use of default values was necessary in order to incorporate a wide range of substances into the risk ranking. To make the risk ranking more valid, it is essential to develop an extended compilation of default values for the individual variabilities and LLEs that result from adverse health effects.

The risk ranking shown in Figure 2 should not be regarded as the priorities for risk reduction. This is not only because the estimated risk levels involve various levels of uncertainty as mentioned above, but also because the priority for risk reduction cannot be determined on the basis of the risk level alone. Risk-benefit analysis, in which the risk reduction that results from a countermeasure is compared with its cost, is considered to be a promising tool for the reasonable prioritizing of countermeasures. Figure 2 should thus be regarded as the prioritizing of substances for which detailed research regarding the efficiency of risk reduction countermeasures should be performed. For the substances that are highly ranked, a more detailed risk estimation and socio-economical evaluation of the countermeasures should be initiated.

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Vitae

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Table 1. The substances evaluated in this study

	via inhalation	via ingestion
carcinogens	benzene formaldehyde radon	arsenic chlordane DDTs dioxins
non-carcinogens	chlorpyrifos toluene xylenes	cadmium methylmercury

Table 2. Default GSD values for individual variabilities.

type of individual variability	GSD value and description
metabolizing rate	1.4 (based on the metabolizing rate of generic chemicals: Masuyama, 1977)
body burden of substances via food	2.2 (based on the body burden of PCB: Masuyama, 1976) reflecting variabilities in exposure level and metabolizing rate
sensitivity	2.7 (based on the methylmercury poisoning: Nordberg and Strangert, 1976)

Table 3. Default LLE values for depressed health statuses.

Health status category [a]		LLE (years) [c]
I	impairment (unable to conduct daily life)	14.3
II	impairment (difficulty in daily life)	6.24
III	chronic illness (with more than 2 diseases [b])	3.27
IV	chronic illness (with one disease [b])	2.01
V	symptoms (convulsion, fatigue, etc.)	1.05
VI	no symptoms	0

[a] based on Berkman and Breslow (1983).

[b] hypertension, asthma, epilepsy, diabetes, cancer, tuberculosis, gastric ulcer, hepatopathy, etc.

[c] derived based on the mortality rates reported by Berkman and Breslow (1983) using life table analysis.

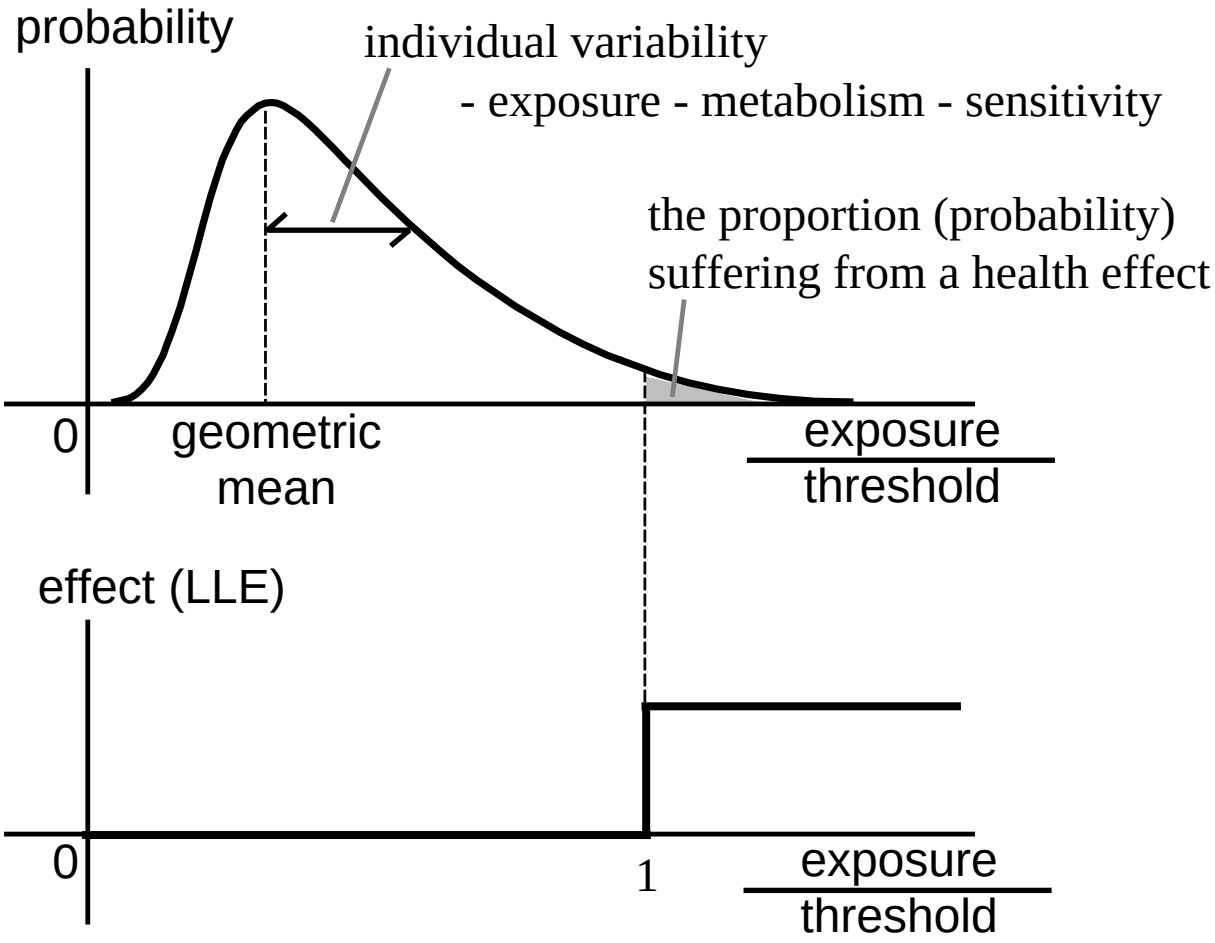

Figure 1. Schematic diagram of the estimation of non-cancer risks.

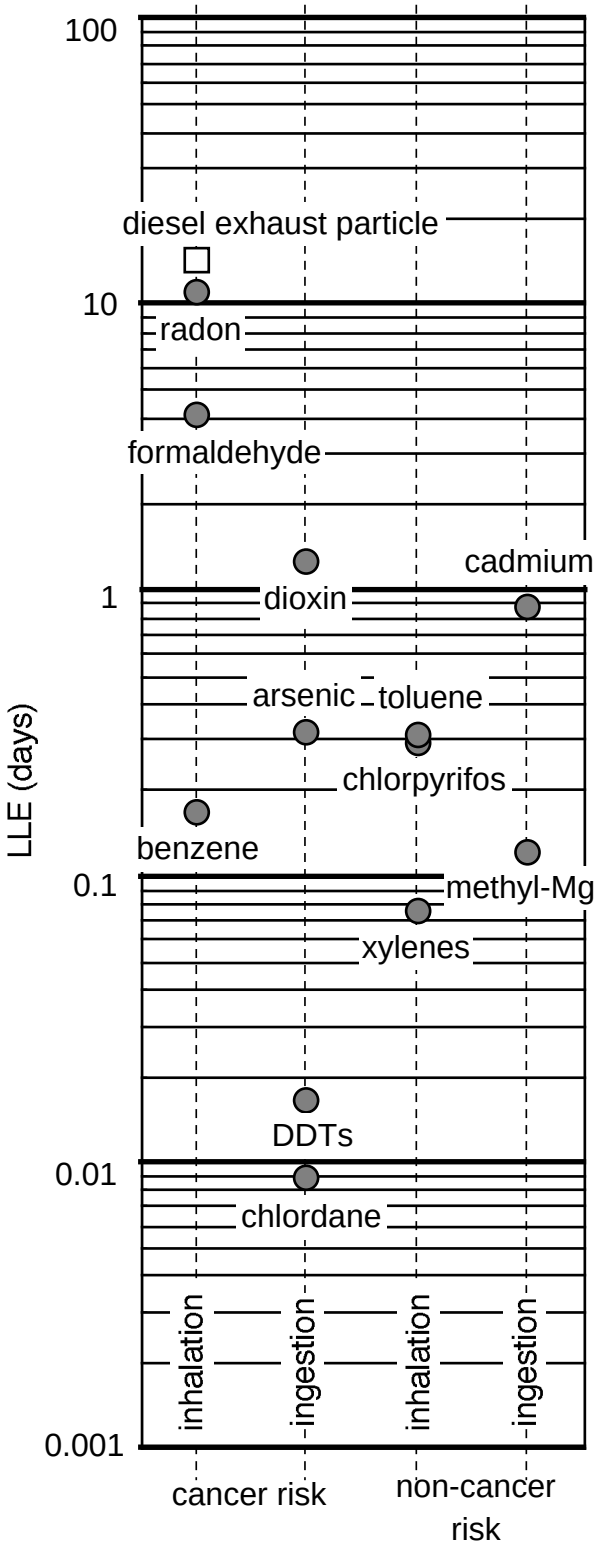

Figure 2. Estimated risk levels of the chemical substances in Japan.