Environmental Risk Evaluation of Chemicals: Achievements and Seeds for Future
---- Development of Metrics for Evaluating Risks ----

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Abstract

Achievements of our research project supported by the JST were introduced and reviewed, focusing on the development of the methodology for estimating risks; human health risks and ecological risks. The usefulness of loss of life expectancy as a metric for evaluating cancer and noncancer risks was demonstrated. To evaluate ecological risks, three metrics, 1/T, logT and T, developed based on the mean extinction time of species (T) were proposed. Then, their implication and feasibility were examined in terms of what ecological system should be conserved and how easily people can understand the implications of metrics. Protocols for estimating human health risks and ecological risks are illustrated.

1. Objective of the research project

Our research project entitled “Establishment of a scientific framework for the

management of toxicity of chemicals based on environmental risk-benefit analysis" started in fiscal year 1996. As can be understood from the title, the project is aimed at developing a scientific framework for the management of chemical use based on risk-benefit analysis. An overview of the project is shown in Figure in the Appendix, together with the following three objectives; 1) to evaluate human health risks from chemical use; 2) to evaluate ecological risks from chemical use, various types of exploitation and fishing; and 3) to balance the risks from against the benefits of chemical use (Nakanishi, 1998).

It must be emphasized here that the objective framework is very different from those that have firmly been established and employed for decision-making in developed countries, such as European countries and the United States. Our project has given special emphasis to the development of the methodologies of risk evaluation by which we can compare quantitatively the risks posed by a broad spectrum of endpoints that differ in severity of impact on human health and the ecological system in terms of resource allocation and risk management. For this purpose, we have proposed loss of life expectancy (LLE) as a single metric for evaluating various types of human health risks, and the probability of species extinction as an another single metric for evaluating various types of ecological risks (Nakanishi, 1995; Gamo et al., 1995). In this paper, we review what our project has achieved over the past five years in the area of development of metrics for human and ecological risk evaluation will be reviewed in terms of the fruits and the seeds for future.

2. Methods for Evaluating Human Health Risks

2.1 *Direct Metrics for Evaluating Human Health Risks*

2.1.1 *Current State*

Although quantitative risk assessment methods are commonly used for regulatory purposes, such methods are not applied for comparing various types of human health risks. Only the fatal effects are generally considered in efficiency analysis such as risk-benefit analysis for evaluating the efficiency of policies. Cancer risk is considered in efficiency analysis, because the excess cancer death due to exposure to a chemical is estimated. However, noncancer risks are not considered in such analysis, because for noncancer endpoints, the result of the risk evaluation is represented in terms of hazard quotient (HQ) which is the ratio of exposure to the safety exposure level, and does not allow estimation of the probability of an adverse effect or even identification of the specific harm that might be expected, shown in Table 1.

Table 1. Outcomes of human health evaluation used in risk analysis

		Endpoint			
		Injury	Cancer	Noncancer	
		Fatal		Fatal	Nonfatal
Common regulatory assessment	Outcomes	Deaths	Deaths	HQ	HQ
	Comparability	○	○	×	×
Epidemiological-based assessment	Outcomes	Deaths	Deaths	Deaths	Hospital Admissions
	Comparability	○	○	○	×
Harvard University	Outcomes	LLE	LLE	LLE*[1)]	Not evaluated
	Comparability	○	○	○	×
Our project	Outcomes	LLE	LLE	LLE	LLE
	Comparability	○	○	○	○

*[1)] Noncancer mortality due to chemical exposure has rarely been evaluated.

However, the risk assessment method based on epidemiological studies has been carried out for traffic-related air pollution and occupational pollution. In such assessment, the fatal effects (mortality) of not only cancer but also noncancer diseases and the nonfatal effects (morbidity) attributable to chemical pollution are estimated. Health outcomes of morbidity are often evaluated in terms of disease incidence or hospital admission rates. Therefore, it was difficult to consider the nonfatal risks in efficiency analysis. In other words, the efficiency of environmental policies was compared and evaluated based on the number of deaths.

Recently, however, " deaths" are considered a misleading metric, since everyone must die sooner or later. To account for prematurity of death, the number of life-years lost becomes a popular metric since it accounts for premature deaths at all ages and since life expectancy information can be obtained from standard life tables. Researchers in the Harvard Center for Risk Analysis (Tengs et al., 1995) compared the cost per life-year saved of more than 500 policies in the USA. In their analysis, values of LLE of respective diseases were not used, but the certain value of LLE determined for each category was used, such as LLE of 30 years for deaths due to occupational disease and injury and 10 years for cancer.

2.1.2 *Our method*

We also proposed LLE as a metric for evaluating human health risks. The characteristic of our proposal is that we use LLE as a metric for evaluating the total risk due to fatal effects and nonfatal effects and that LLE values differ depending on the disease or symptom. Our proposal has met severe criticism because the nonfatal effects are not considered in the analysis. This criticism may be due to a misunderstanding of our idea and this

understanding must come from the background where the metric of LLE has been widely used to evaluate fatal risks so far. Our basic standpoint is that the mortality of a disease reflects, to some extent, physical and emotional burden due to the disease and that the outcome in terms of death is a reflection of fatal and nonfatal effects. Even in the case where the mortality due to mild symptom is not accountable or known to us, the symptom is regarded as the decrease in health status which can be related to LLE. For rating the decrease in health status, Gamo et al. (1995) applied Cornell medical index scores, which was found to relate to increase in mortality based on the epidemiological study on paper industry workers.

The protocol for estimating risk in terms of LLE

1) Cancer risk

1-1) Individual risk

risk(E)(in terms of probability) = (cancer potency)＊(E)

RISK(E)(in terms of LLE) = risk (probability)＊12.6 (years)

E is exposure level.

1-2) Aggregate population risk

Population risk = ∫ probability（E）×RISK（E）dE

Probability(E) is probability of individuals with exposure of E and follows a statistical distribution, such as a log-normal distribution.

2) Noncancer risk (aggregate population risk)

2-1) When dose-response relationship is available,

RISK (in terms of LLE)= ∫ probability（BB）×Effect（BB）dBB

Probability(BB) is probability of individuals with body burden of BB which reflects individual variability in exposure and metabolizing rate, and, follows a statistical distribution.

Effect（BB）＝the magnitude of adverse health effects in individuals with body burden of BB in terms of LLE

2-2) When only NOAEL for human is available,

risk＝probability（MOE > 1）

NOAEL and E are independent, and probability(NOAEL) and probability(E) follow respective statistical distributions.

RISK＝risk×severity (LLE)

3) The severity-values of disease: refer to the paper by Gamo et al.(2001).

4) The values of parameters regarding individual variability used for our studies are listed in Table A1 in the Appendix.

Gamo et al.(2001) estimated human health risks of the Japanese population due to 12 chemicals in terms of LLE. The risks estimated include cancer and noncancer, and nonfatal ones. The use of LLE as a metric enabled us to compare various types of risks. Gamo et al. report the details of the results and risk estimation methods in their paper (Gamo et al., 2001)

The protocol for estimating human health risks is shown in the column, where the aggregate population risk means the total risk for the entire population at risk. In addition, noncancer risk is defined as probability that margin of exposure (MOE), the ratio of the no-observed-adverse-effect level (NOAEL) to the exposure level is more than 1, when the dose response relationship is not available. Furthermore, it is noteworthy that the risk due to nongenotoxic carcinogens is calculated similarly as noncancer risk.

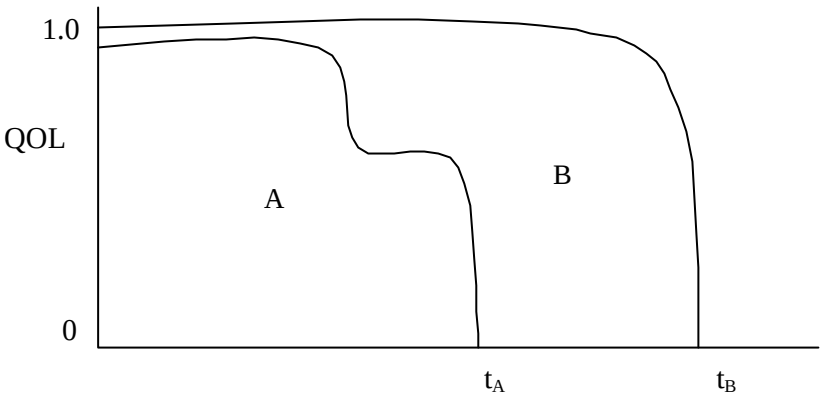
As shown above, LLE is a useful metric for evaluating fatal and nonfatal risks and more important, it is an objective and scientific one. However, considering that people in developed countries are becoming more and more sensitive to even mild symptoms, it may be true that LLE is too insensitive to mild symptoms. Although we were successful in presenting the framework, we failed to collect copious data on disease severity in terms of LLE. This is partially because elaborate work is necessary to collect data regarding LLE. Therefore, as our next step, we will improve the metric of LLE so that it will be more sensitive to mild symptoms and easier to collect or measure. Another point that we must consider in the future is how to incorporate people's preference or choice into the metric.

2.2 *Indirect Metrics for Evaluating Human Health Risks*

An alternative approach for evaluating risks is to establish monetary values for specific damages within the context of economic markets. This approach is used to evaluate fatal effects and nonfatal effects. The value of WTP (willingness to pay) by contingent market method is obtained by asking people to state the maximum price they would be willing to pay to eliminate a certain risk, which is thought to represent the magnitude of the risk in monetary unit. This approach has an advantage of being easily integrated into cost-benefit analysis of policies. Another advantage of this approach is that people's preference or acceptance is incorporated into the results obtained. Despite such good points, serious drawbacks are pointed out; 1) the accuracy of the results is not guaranteed, 2) the results are vulnerable to the method used for interview, and 3) the results are vulnerable to rumor or superstition. Although this metric is a good tool for integrating fatal risks and nonfatal risks, we did not use it for certain reasons, as Oka states in his paper (2001). In the future, we should examine the feasibility of the metric of WTP for evaluating risks of mild symptoms, because people's preference should be given more consideration in evaluating mild symptoms. .

As a metric to combine various kinds of risks, the use of quality-adjusted life year (QALY) is drawing expert's attention in the area of environmental policy studies. The use of

QALY has recently begun for evaluating environmental policies, though it has been widely used for establishing and evaluating medical policies over the past two decades. The concept of QALY is illustrated in Figure 1.



QALY(A) = area of A = $\int_0^{t_A} QOL(A)dt$

QALY(B) = area of B (including area of A) = $\int_0^{t_B} QOL(B)dt$

Risk = Loss of QALY = QALY(B) − QALY(A) (in terms of year)

Figure 1. Concept of QALY

QALY is a metric of health outcome that assigns to each period of time a weight, ranging from 0 to 1, corresponding to the quality of life (QOL) during that period, where a weight of 1 corresponds to perfect health and a weight of 0 corresponds to death. The number of QALY that is an integrated value of QOL for a lifetime represents the number of healthy years of life that are valued equivalently to the actual health outcome. QALY is competent for evaluating and comparing nonfatal risks, and more important, it reflects partially people's preference and partially the objective state of deteriorated human health. In addition, it is not so difficult to combine LLE with QALY, although some problems remain to be solved. How to use QALY for human health risk evaluation in the context of environmental policy and how to establish QOL weights data in Japan are our future problem.

3. Ecological Risk Evaluation Method

3.1. *Introduction*

As I have stated in the section 1, one of our objectives was to develop methods for evaluating ecological risks using the metric of probability of species extinction when I started

this project. I proposed to use species extinction as the endpoint for ecological risk evaluation for the following three reasons: 1) the extinction of species is an event that everyone wants to avoid, 2) the probability of species extinction can be used for evaluating ecological effects due to activities other than the use of chemicals, such as exploitation or fishing, and 3) the consequences of ecological effects should be evaluated in terms of the event that would occur in the future (Nakanishi, 1995)

Generally, ecological-effect models are classified as organism-level, population and ecosystem or landscape models. According to this classification, the models we developed in the project are classified as population models and the food-web ones as ecosystem models (Miyamoto et al. 1998, Naito et al., 1999, 2000 and Murata et al. 2001)

The extinction probability is represented by the inverse of the mean extinction time, where the mean extinction time (T) is defined as the expected time to extinction of a population. In our project, Oka and Matsuda (Oka et al., 2000) evaluated the ecological risk posed by the development of a wetland by taking the sum of the increments in extinction probabilities of the species living in the wetland weighted by the importance from the viewpoint of biodiversity conservation.

However, in the course of our research, we have been taught that the metric of 1/T is useful for the conservation of endangered species, whereas the metric of T or logT may be more useful for protecting a stable habitat. The major merit in using latter metric is that decrements of T or logT can be related to the loss of carrying capacity. Since Iwasa discusses this point in detail (Iwasa et al., 2001), I will introduce here the ecological risk evaluation method by means of the latter metric, developed by Iwasa et al. and Tanaka et al., focusing on the procedure for estimating the ecological risk.

3.2 *Approach by Iwasa et al.*

Iwasa et al. (Iwasa 1998; Hakoyama and Iwasa 1998; Hakoyama and Iwasa 2000; Hakoyama, Iwasa and Nakanishi 2000; Iwasa, Hakoyama, Nakamaru, and Nakanishi 2000) proposed a simple standard model of population dynamics, in which the population dynamics (dX/dt, X is population size) is described using three parameters; intrinsic growth rate (r_s), environmental carrying capacity (K) and intensity of environmental fluctuation (σ_e) (equations are shown in their paper, 2001). Given the values of r_s, K and σ_e, analytical solution of T is obtained. Then, the effect of chemical (δ) was incorporated into the model. Using the model, $\log \overline{T}$ ($\bar{}$ indicates the natural condition) and logT' (' indicates the condition under chemical stress) are calculated, where the values of $\overline{r_s}$, r_s' and $\overline{K}$ are given.

They found that the decrease in the fixed fraction of carrying capacity loss causes the same decrease in logT, irrespective of K. The implication of loss of carrying capacity is easier to understand intuitively than that of 1/T for a long-term sustainable population. Therefore, they

intended to evaluate ecological risk in terms of ΔlogT and thus in terms of the corresponding ΔK /K., which is called the risk equivalent. The ΔK is an imaginary decrements in carrying capacity due to chemical exposure and differs from the true decrements (ΔK=K'– $\overline{K}$ =– δ /r_s). The corresponding approximate value of $\Delta K / \overline{K}$ is obtained, using the following equation,

$$\Delta \log T \approx 1/CV^2 \Delta \log K ,$$

where CV^2 is the squared coefficient of variation of population size. It is noteworthy that many assumptions are made to obtain the final solution in the procedures above. Regarding these assumptions, one should refer to papers by Y. Iwasa et al.(2001).

Protocol for obtaining risk equivalent (approach by Iwasa et al)

1) To calculate log$\overline{T}$ and logT' , where the values of $\overline{K}$, $\overline{r_s}$, CV^2 and r_s' are needed.
2) To calculate $\Delta K / \overline{K}$ based on ΔlogT (=logT'–log$\overline{T}$)
3) To obtain the value of r_s', values of elements in the Leslie matrix under chemical stress are needed.

According to the protocol written above, Nakamaru et al. (2001) estimated the ecological risk of herring gull and sparrow hawk due to DDT in terms of ΔlogT and the resultant $\Delta K / \overline{K}$. One can find the procedures and results of this research in their paper.

3.3 *Approach by Tanaka et al.*

Tanaka and Nakanishi (1998a, 1998b, 2000, 2001) (Tanaka 1998; Tanaka 2000) developed the risk evaluation method based on the approximate formula of the mean extinction time (T) (the scaling law; c.f. Lande 1998). According to the scaling law, T is described by means of three parameters; carrying capacity (K), intrinsic growth rate (r_i) and environmental variation of r_i (v). Introducing approximation and given the value of r_i' (under chemical stress), ΔlogT and the corresponding ΔK , the risk equivalent, are obtained by ,

$$\Delta \log T \approx 2 \log \overline{K} \times \Delta s$$

$$\Delta \log K \approx \Delta \log T / 2 \ (\bar{s} + \Delta s - 0.5) ,$$

where $\Delta r_i = r_i' - \overline{r_i}$, and Δs is roughly equal to $\Delta r_i / \bar{v}$, as the change of v due to chemical exposure is thought to be small.

In addition, they found the following regressions which relate r_i' to acute toxicity LC50 for zoo planktons such as daphnia species,

$$r_i'(x) = \overline{r_i} [1-(x/\alpha)^{\beta}] \quad (\beta = 1.84)$$

$$\log \alpha = c + b \times \log[LC50] \quad (b=0.843,\ c=1.562),$$

where b and c are constants and x is the concentration of the chemical (Tanaka and Nakanishi;

2001).

This finding is useful from a practical viewpoint, because generally speaking it is time- and labor-consuming to obtain r_i'- values at several concentrations of chemicals.

The protocol for obtaining $\Delta T/T$ and corresponding $\Delta K/K$ for planktons (approach by Tanaka et al.)

1) To calculate r_i' at the exposure concentration of the chemical x, using LC50.
2) To calculate $\Delta \log T$ assuming the default values of $\overline{K} = 10^6$, $\overline{r_i} = 0.3$, $\overline{v} = v' = 0.03$
3) To calculate $\Delta \log K$、and consequently $\Delta K/K$
4) To calculate $\Delta T/T$

Table2 shows the predicted percentage reduction of T due to exposure to chemical of concentrations of 1/10 and 1/100 of the acute toxicity LC50. Figures in parentheses indicate percent reduction of the carrying capacity corresponding to the percentage reduction of T. In response to an exposure concentration of 1/100 of LC50, T rarely decreased by more than 1% (the mean decrease rate is 0.22%). The same amount of reduction in T would result from a reduction of the carrying capacity only by 0.012% on average if the carrying capacity were 10^6.

The present results are limited to plankton populations. Nonetheless, it gave objective and clear meaning of the LC50-value. The result indicates that such a risk estimation method is useful to know the impact of a chemical on the ecological system. And if we can obtain values of the basic parameters for other species, we can examine the relationship between the individual-level toxicity data such as LC50 and their ecological impacts.

3.4 *Significance of our research and problems*

Our research project has developed a scientific framework for estimating the change in T due to chemical exposure. Based on T, three kinds of metrics, (1/T), T/T and logT, were considered, and one of them was chosen depending on the situation of species at issue. Among the three, which one is the most appropriate depends on the goal of the policy regarding ecological system conservation. In addition, we must choose metrics in terms of how to incorporate the estimated risk into risk-benefit analysis.

Table 2. Predicted reductions in mean extinction time among planktons.
(Tanaka and Nakanishi, 2000)

Test species	Chemicals	LC_{50}	α	ΔT% (ΔK%)	
				[LC_{50}/10]	[LC_{50}/100]
D[1]. *pulex*	Cadmium	62.0	16.4 [10]	69.4 (6.07)	1.18 (0.062)
E[2]. *affinis*	Kepone	40.0	23.1 [11]	22.0 (1.30)	0.25 (0.013)
E. affinis	Dieldrin	23.0	6.1 [20]	69.2 (6.04)	1.17 (0.062)
D. magna	Copper	85.1	111.5 [21]	4.7 (0.25)	0.05 (0.003)
D. magna	Copper	83.4	98.1 [21]	5.8 (0.32)	0.06 (0.003)
B[3]. *rubens*	PCP	0.2	0.3 [22]	3.6 (0.19)	0.04 (0.002)
B. rubens	4-chloroaniline	100.0	81.7 [22]	11.7 (0.65)	0.12 (0.007)
B. rubens	4-nitrophenol	6.3	6.2 [22]	8.2 (0.45)	0.09 (0.005)
D. magna	Disulfiram	12.0	30.5 [23]	1.3 (0.07)	0.01 (0.001)
D. magna	TMTU	75000.0	101500 [23]	4.4 (0.12)	0.05 (0.002)
D. magna	Zineb	89.0	200.8 [23]	1.6 (0.09)	0.02 (0.001)
D. magna	Cadmium	24.0	29.7 [24]	5.3 (0.29)	0.05 (0.003)
D. magna	Cadmium	24.0	57.2 [24]	1.5 (0.08)	0.01 (0.001)
M[4]. *bahia*	Mercury	3.5	1.46[29]	36.3 (2.35)	0.45 (0.024)
D. magna	Copper	86.5	150.5 [30]	2.7 (0.14)	0.03 (0.001)
D. pulex	Copper	86.0	84.1 [30]	8.3 (0.46)	0.09 (0.005)
D. parvula	Copper	72.0	63.1 [30]	10.2 (0.57)	0.11 (0.006)
D. ambigua	Copper	67.7	87.3 [30]	4.9 (0.26)	0.05 (0.003)
L[5]. *squammata*	DDT	5.0	4.77 [31]	8.6 (0.47)	0.09 (0.005)
L. squammata	DDT	5.0	3.2 [31]	18.3 (1.06)	0.20 (0.011)
M. bahia	Nickel	508.0	148.6 [32]	62.0 (4.99)	0.96 (0.051)
D. magna	Metals (TU)	1.8	3.4 [33]	2.3 (0.12)	0.02 (0.001)
D. magna	Metals (WQC)	0.6	1.2 [33]	2.1 (0.11)	0.02 (0.001)

1) *Daphnia*, 2) *Eurytemora*, 3) *Brachionus*, 4) *Mysidopsis*, 5) *Lepidodermella*.
ΔT%：percent reduction of mean extinction time ($|\Delta T|/T \times 100$).
Δ*K*%：percent reduction of equilibrium K values that would cause the same level of extinction risk.
Parameter values: $K = 10^6$, $\bar{r}_i = 0.3$, and $v = 0.03$.

Although many problems remain, it is highly important to accumulate examples of ecological risk evaluation carried out using our framework. For this purpose, values of parameters must be examined more carefully, and must be intensively collected and compiled. However, it is unlikely that we can collect copious data of parameters regarding biological

systems or species, which are needed for risk evaluation. Neither us nor other groups can do so. Therefore, we are forced to find other possible ways to collect such data. The way of estimating and producing values of parameters supported by biology and ecology may be open to us. This task must be one of our future subjects.

Our research goal of this project is to carry out efficiency analysis of environmental policies such as risk-benefit analysis. Oka explains and discusses this (2001).

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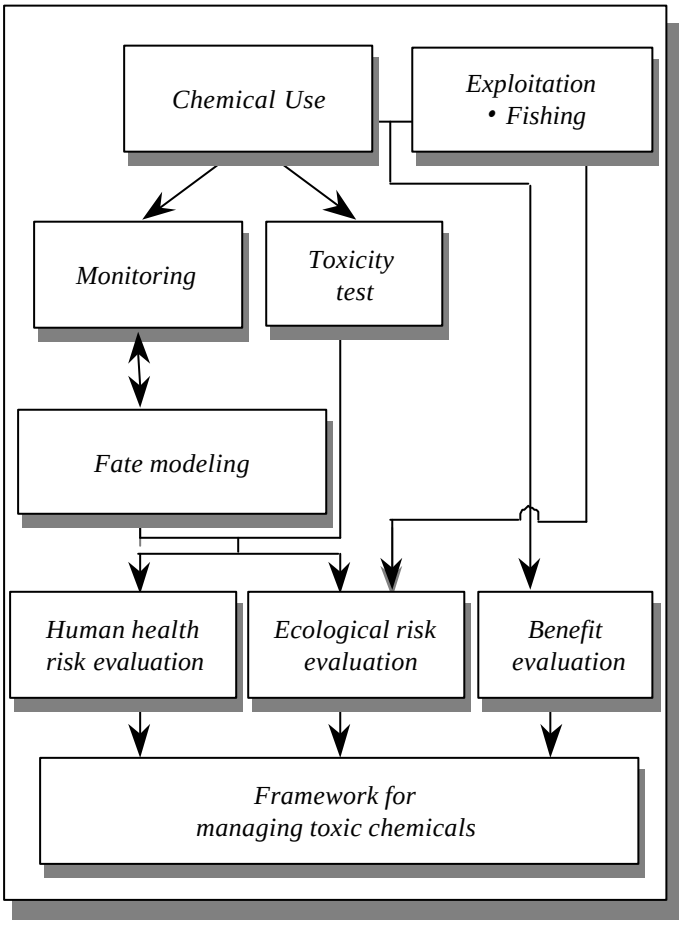
Appendix



◆***Monitoring:*** monitoring of chemicals targeted for the project, in various environmental media.

◆***Fate modeling:*** development of models for estimating the behavior of chemicals in various environmental media.

◆***Human health risk evaluation:*** development of methodologies to evaluate human health risks in terms of Loss of life expectancy (LLE).

◆***Ecological risk evaluation:*** development of methodologies to evaluate ecological risks in terms of probability of species extinction.

◆***Benefit evaluation:*** evaluation of benefits associated with the use of each chemical such as economical benefits, convenience accruing from its use and conservation of resources.

◆***Final proposal:*** proposal of a framework for managing toxic chemicals based on risk-benefit analysis.

Figure A1. Project Overview (Nakanishi, 1998)