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Regulatory Aspect of Risk Assessment and Management

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ABSTRACT *: Risk assessment is useful tool making good decisions on the risks of certain hazardous compound and suggests safe margin through scientific process using toxicological data, statistical tool, exposure value and relevant variants. The goal of risk management is to protect the public health from hazardous compound based on result of risk assessment having reality. For the suggestion of exact managing information, risk assessment must be designed to represent a "plausible estimate" of the exposure to the individuals and to minimize uncertainty. Risk assessment methodology and knowledge are expected to change more rapidly than before and up-to-date methodology should be applied in regulatory aspects through the Agency. For the useful application of risk assessment, the communication between the risk assessor and the risk manager is needed before the initiation of the risk assessment and upon its completion. Generally, the risk assessment itself as a practical tool in the regulatory decision making process would be regarded with social economic impact.*

Key Words *: Risk assessment, Safety margin, Plausible estimate, Uncertainty, Regulatory decision*

I. INTRODUCTION

Risk assessment was defined as "the determination of the probability that an adverse effect will result from a defined exposure" while risk management was defined as "the process of weighing policy alternatives and selecting the most appropriate regulatory action based on the results of risk assessment and social, economic, and political concerns by the NAS (National Academy of Sciences, 1983)". Earlier the American Conference of Governmental Industrial Hygienists (ACGIH) had set threshold limit values for workers and the U.S. Food and Drug Administration (FDA) had established acceptable daily intakes for dietary pesticide residues and food additives.

Product of risk assessment includes qualitative information on the strength of the evidence and the nature of the outcomes, quantitative assessment of the exposure and the potential magnitude of the risks, and a description of the uncertainties in the conclusions and estimates. Risk assessment has matured into a powerful analytical tool, which is finding ever-wider applications in the arena of policy making and regulation. The principal focus of its development to date has been on the technical challenges of characterizing and modeling the environmental behavior and biological action of chemicals. Socio-political context have been generally neglected (Eduljee, 2000). Because a high quality risk assessment process is one of the essential scientific components in rational regulatory decisions, the risk assessment process must be subjected to the highest peer review standards as well as be relatively isolated from outside influences such as politics, economic consideration, etc. There is a definite need for communication between the risk assessor and the risk manager before the initiation of the risk assessment and upon its completion.

This paper explained general methodology of risk assessment and introduce examples be applied at management in regulatory aspects using result of risk assessment for interpretation of relationship between risk assessment and risk management.

II. METHODOLOGY OF RISK ASSESSMENT

The framework of risk assessment which is composed with four steps as hazard identification, exposure assessment, dose-response assessment and risk characterization, has been applied most frequently for the assessment of cancer risks; currently, noncancer endpoints are also receiving the similar type of evaluation using such framework approaches.

The methodology of risk assessment is largely based on two types as nonthreshold approach and threshold approach and produced toxicity value is combined with human exposure dose to estimate risk value.

1. Cancer risk assessment using nonthreshold approach

The Cancer risk assessment is applied for assessment of hazardous compound having obvious evidence on the carcinogenic effect in step of hazard identification which characterizes the innate toxic effects of agents. The carcinogen classification ranging by U.S. Environmental Protection Agency (U.S.EPA) and International Agency for Research on Cancer (IARC) were listed in Table 1 based on the extent that the substance has been to be carcinogenic in animals or humans (or both).

Evidence is sufficient in humans on the basis of an epidemiology study that clearly demonstrates a causal relationship between exposure to the substance and cancer in humans. Sufficient animal evidence consists of an increase in cancer in more than one species or strain of laboratory animals or in more than one experiment. Data from a single experiment can also be considered sufficient animal evidence if there was a high incidence or unusual type of tumor induced.

Currently, U.S.EPA revised cancer assessment categories as above Table 1 from traditional classification (A, B, C, D, E) having purpose of assessing childrens risk and considering changed method and knowledge.

The carcinogenic evaluation is a two step process (1) dose scaling for conversion of animal doses to equivalent human doses and (2) extrapolation from high doses (normally used in animal tests) to the lower dose levels to which the general population are usually exposed, mathematical models are used.

For conversion of animal doses to equivalent human doses, either the comparative ratio of body weights or differences in surface area can be used to extrapolate effective doses between animals and humans (Table 2).

Species dose scaling is accomplished further by assuming that animals and humans are equally susceptible (in terms of extra risk) when the dose is measured in the same units for both species.

Dose (mg/kg/day) administered to animals was converted to equivalent human average daily lifetime dose (mg/kg/day) based on the assumed surface area equivalency and the assumption that surface is proportional to body weight to the 2/3 power before suggestion of body weight conversion factor to the 3/4 power by U.S.EPA.

Use of surface area correlation for dose conversion has been under reevaluation since there has not been agreement between the U.S.EPA and U.S.FDA on the issue.

Table 1. U.S.EPA and IARC cancer assessment categories

U.S.EPA	IARC	
· Carcinogenic to humans	**1**	Agent is carcinogenic
· Likely to be carcinogenic to humans	**2A**	Agent is probably carcinogenic
· Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	**2B**	Agent is probable carcinogenic
· Data are inadequate for an assessment of human carcinogenic potential	**3**	Agent is not classifiable as to Carcinogenicity
· Not likely to be carcinogenic to human	**4**	Agent is probably not carcinogenic

Table 2. Species dose scaling factors for conversion of animal doses to equivalent human doses

Assumption	Equation
• Surface Area Equivalency (2/3 power) • Body Weight Equivalency (3/4 power)	• $D_H = D_A[BW_A/BW_H]^{1/3}$ • $D_H = D_A[BW_A/BW_H]^{1/4}$
D_H; human equivalent dose, mg/kg/day D_A; experimental animal dose, mg/kg/day BW_A; body weight in animals, kg BW_H; body weight in human, kg	
• Animal Dose 2 mg/kg/day; 2/3 power → Human Dose; 0.342 mg/kg/day 3/4 power → Human Dose; 0.532 mg/kg/day	

(U.S.EPA, 1999)

The U.S.FDA used simple body weight conversion parameters rather than surface area correction. A risk value derived using 3/4 power conversion factor would be approximately two to three times lower than that derived using 2/3 power conversion factor.

The key risk assessment parameter derived from the carcinogen risk assessment process as used by the U.S.EPA is the "slope factor" or "cancer potency" induced in extrapolation process from high doses to low lose.

A slop factor is a plausible upper bound estimate of the probability that an individual will develop cancer if exposure is to a chemical for a lifetime of 70 years and quantitatively defines the relationship between dose and response.

Fig. 1 illustrates a dose-response relationship for a carcinogen (ex; chloroform, dioxin) and then demonstrates how a mathematical model extrapolates from observed data to predict risk at low doses. As illustrated, the low dose risk extrapolation assumes linearity with no threshold for the effect.

Several mathematical models have been used to extrapolate from carcinogenic results observed at high doses to predict risk at low doses. The model chosen is based on an understanding of the mechanism for the carcinogenic response. The EPA default model is the linearized multistage model (LMS). The LMS model yields the slope factor, also known as the q_1^* (pronounced Q-on-star).

Other mathematical models that have been used are listed in Table 3.

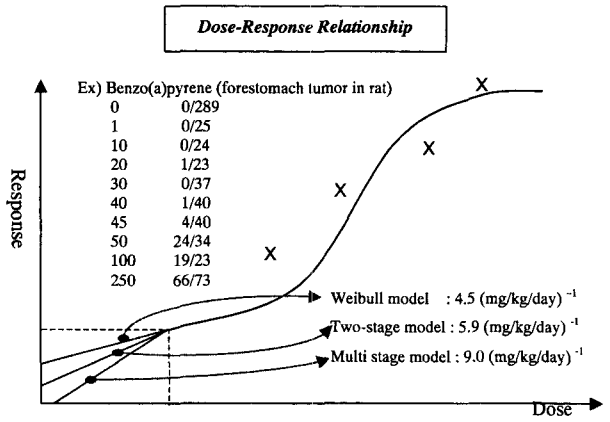

Fig. 1. Extrapolation from high dose to low dose for carcinogens.

If cancer potency to liver cancer incidence of some carcinogen is 1.56×10^{-4} (pg/kg/day)$^{-1}$ and chronic daily intake is 3.6 pg/kg/day, excess cancer risk value would be estimated as following.

*Excess cancer risk
= Cancer potency (mg/kg/day)$^{-1}$
×Chronic daily intake (mg/kg/day)
$=1.56\times10^{-4}$ (pg/kg/day)$^{-1}\times3.6$ pg/kg/day
$= 5.6\times10^{-4}$

For carcinogenicity, the probability of an individual developing cancer over a lifetime is estimated by multiplying the slop factor (mg/kg/day)$^{-1}$ for the substance by the chronic daily intake (mg/kg/day).

Potential carcinogenic risks are expressed as increased probability of developing cancer during a per-

Table 3. Mathematical models used for assessment of nonthreshold effects

Mathematical Models	Equation and Theory
Linearized multistage model	$P(d) = 1 \exp(-q_0 - q_1{}^d - \ldots - q_k{}^{dk})$ $Q_1 \geq 0$, I = 0, . . . k, k = # of dose groups -1 - Assumes that there are multiple stage for cancer - Fits curve to the experimental data - Linear from upper confidence level to zero
One hit model	$P(d) = 1 - \exp(- bd)$ - Assumes there is a single for cancer and that are molecular or radiation interaction induces malignant change - Very conservative
Probit model	$P(d) = a_0 + (1\ a_0)(a_1 + a_2 \log_{10} d)$ $0 \leq a_0 \leq 1$, $a_2 \geq 1$ - Assumes probit (log-normal) distribution for tolerance of exposed population - Appropriate for acute toxicity; questionable for cancer
Weibull model	$P(d) = 1 \exp(-a_0 - a_1 d^{a2})$ $Q_1 \geq 0$, i = 0,1 $a_2 \geq 1$ - Assumes either that tumors are fatal or that tumor are incidental. - Flexibility in describing different data set

son's lifetime. For example, a 10^6 increased cancer risk represents an increased lifetime risk of 1 in 1,000,000 of developing cancer.

This risk is considered a conservation estimate since the upper bound estimate for the slop factor is used, with the "true risk" likely being less.

Individuals are often exposed to substances by more than one exposure pathway, for example, drinking of contaminated water ingestion of contaminated food and inhalation of contaminated dust. The total exposure to various chemicals via various routes will equal the sum of the exposures by all pathways.

For carcinogens, the cancer risk for the same subpopulation can be added for each exposure pathway contributing to exposure, assuming additively and if necessary correcting for exposure periods.

2. Non-cancer risk assessment using threshold approach

Traditionally, the acceptable daily intake (ADI) values are used by the World Health Organization (WHO) for pesticides and food additives to define "the daily intake of chemical, which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at that time" (WHO, 1962).

The basic concept is that an ADI is determined by applying safety factors (to account for the uncertainty in the quality of the data) to the highest dose in human or animal studies that has been demonstrated not to cause toxicity. The U.S.EPA has slightly modified the ADI approach for their purposes. For chronic non-carcinogenic effects, the U.S.EPA acceptable safety level is known as the reference dose (RfD). The RfD is defined as "an estimate of a daily exposure level for the human population, including sensitive subpopulations that are likely to be without an appreciable risk of deleterious effects during a lifetime".

Reference doses and ADI values typically are calculated from NOAEL values by dividing by uncertainty (UF) and/or modifying factors (MFs) (U.S.EPA, 1991).

- ADI = NOAEL or LOAEL/($UF_{1 \cdots 3} \times MF$)
  - UF_1 10 from animals to humans
  - UF_2 10 human variability
  - UF_3 10 LOAEL instead of NOAEL
  - Modifying factor $1 < MF < 10$
- RfD = NOAEL or LOAEL/($UF_{1 \cdots 5} \times MF$)
  - UF_1 10 from animals to humans
  - UF_2 10 human variability
  - UF_3 10 less than chronic data
  - UF_4 10 LOAEL instead of NOAEL
  - UF_5 10 incomplete data base
  - Modifying factor $1 < MF < 10$
- NOAEL : No Observed Adverse Effect Level
- LOAEL : Lowest Observed Adverse Effect Level

Table 4. Value difference between ADI and RfD

(mg/kg/day)

Pesticide	ADI	RfD
Bentazon	0.1	0.03
Carbaryl	0.01	0.1
Cypermethrin	0.05	0.01
Dichlorvos	0.004	0.0005
Ethion	0.002	0.0005
PCNB (Quitozene)	0.007	0.003
Lindane	0.008	0.0003

(IRIS/U.S.EPA and FAO/WHO)

As the above illustrated, there are some differences in induction process of ADI and RfD. Table 4 shows distinct value difference between ADI and RfD.

If some study is an epidemiology study with a NOAEL of 15 mg/kg/day, RfD is 1.5 mg/kg/day

$$*RfD = \frac{15 \text{ mg/kg/day}}{10 \text{ (human variability)}} = 1.5 \text{ mg/kg/day}$$

And, if some study is a subchronic study in rats with LOAEL of 15 mg/kg/day, RfD is 0.0015 mg/kg/day.

$$*RfD = \frac{15 \text{ mg/kg/day}}{10 \times 10 \times 10 \times 10} = 1.5 \times 10^{-3} \text{ mg/kg/day}$$

10 : from animal to human
10 : human variability
10 : LOAEL instead of NOAEL
10 : less than chronic data

RfDs can be derived for several types of toxic effects, including chronic oral, chronic inhalation, and developmental toxicity.

But, the NOAEL approach has been criticized in several areas, including the following; The NOAEL must by definition be one of the experimental doses tested, once it is identified, the rest of the dose-response curve is ignored, experiments that test fewer animals result in larger NOAELs and thus larger ref-

erence doses, rewarding testing procedures that produce less certain rather than more certain NOAEL values, and the NOAEL approach does not identify the actual responses at the NOAEL and will vary based on experimental design, resulting in regulatory limits set at varying levels of risk.

Because of these limitations, an alternative to the NOAEL approach, the benchmark dose (BMD) method, was proposed by Crump (1984).

The benchmark dose (BMD) is defined as a lower confidence limit corresponding to a moderate increase in risk (1 to 10%) above the background risk. Crump (1984) suggests that the BMD could be used to replace the no observed adverse effect level (NOAEL) for noncancer effects in the regulatory process for setting acceptable daily intakes (ADI) for human exposure to potentially toxic substances. A workshop convened by the U.S.EPA and the American Industrial Health Council (AIHC) to evaluate the benchmark approach identified as an obstacle to implementing the benchmark approach the fact that essentially different quantitative methods must be applied to continuous and quantal data (AIHC, 1995). Based on a study review, a NOAEL or BMD for the critical effect is defined, and then a RfD can be derived. In quantitative risk assessment, BMD methodology holds some distinct advantages over the traditional NOAEL method when determining RfDs. There are many discussion for comparison of the traditional NOAEL approach with BMD method. It was reported that the 5% BMD (BMD_5) was similar to the NOAEL for most datasets, but the 1% effective dose had large confidence intervals and hence the BMD could not be estimated accurately (Auton, 1994). Table 5 shows process for induction of BMD.

Figure 2 shows how a benchmark dose is calculated by using a 5 percent benchmark response and a 95 percent lower confidence bound on the dose.

If 0.17 mg/kg/day of BMD from chronic rat study is used as an alternative to the NOAEL value for RfD calculations.

Thus, the RfD would be 0.0017 mg/kg/day.

$$\bullet \text{ RfD} = \frac{\text{BMD}}{\text{UF}} = \frac{0.17 \text{ mg/kg/day}}{10 \times 10} = 0.0017 \text{ mg/kg/day}$$

If a RfD to reproductive toxicity of some noncarcinogen is 0.0002 (mg/kg/day) and chronic daily intake is 7.2×10^{-5} (mg/kg/day), hazard index (HI) would

Table 5. Induction of BMD using quantal and continuous data

Continuous Data	• Assumed dose-response data	
	(Dose)	(Clinical level)
	0 mg/day	110.1±2.8
	250	118.5±3.2
	500	125.0±3.6
	• Selected model and equation	
	Power Mean Model	
	$\boldsymbol{F(d) = q_0 + SIGN \times (q_0 (d - d_0)^{q2})}$	
	$F(d)$: Mean response among animal subjects to dose d	
	$SIGN$: the direction of adversity	
	D_0 : threshold on dose	
	• Estimated BMD : 8.65 mg/day	
Quantal Data	• Assumed dose-response data	
	(Dose)	(Incidence)
	0 mg/day	2/36
	10	3/34
	100	8/28
	1000	18/30
	• Selected model and equation	
	Weibull Model	
	$\boldsymbol{P(d) = a_0}$ *when* $d \leq d_0$	
	$\boldsymbol{P(d) = a_0 + (1 - a_0) \times (1^{-e^{-a1(d-d0)a2}})}$ when $d > d_0$	
	$P(d)$ = probability that an effect will occur in an animal Subject to dose d	
	a_0 : background term	
	d_0 : threshold on dose	
	• Estimated BMD : 0.65 mg/day	

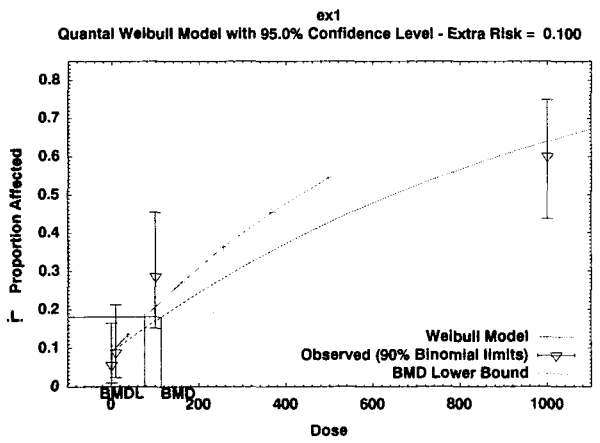

Fig. 2. Induction of BMD using Bench_C program.

be estimated as following.

$$\text{*Hazard Index} = \frac{\text{Chronic daily intake}}{\text{Reference dose}} = \frac{7.2\times10^{-5}}{0.0002} = 0.36$$

For noncancer effect, the exposure level is compared with a RfD derived for similar exposure periods. The comparison provides a ratio of exposure to toxicity which is referred to as the "non-cancer hazard index".

If noncancer hazard index is below than 1, we can assume that occurrence of regarded adverse health effect would not be expected.

This is a simplistic approach and the serve limitation and uncertainties are acknowledged by the EPA and the HI approach is simply used as a screening approach.

III. APPLICATION OF RISK ASSESSMENT IN REGULATORY ASPECT

Risk characterization presents the estimates of potential carcinogen risk and noncarcinogen hazards posed by hazardous compounds.

For known or suspected carcinogens, acceptable exposure levels are concentration levels that represent an excess upper bound lifetime cancer risk of 10^{-5} to 10^{-6}, with a 10^{-6} increased cancer risk as the point of departure. Cancer risk below 10^{-6} usually does not require an emergency response.

Figure 3 shows application example of risk assessment result using nonthreshold approach in drinking water regulation by WHO (1996).

Currently, WHO suggested 200 ug/*l* to chloroform guideline value for drinking water based on cancer risk of 10^{-5} as acceptable risk goal. This value is based on extrapolation of the observed increases in kidney tumors in male rats exposed to chloroform in drinking-water for 2 years, although it is recognized that chloroform may induce tumors through a non-genotoxic mechanism.

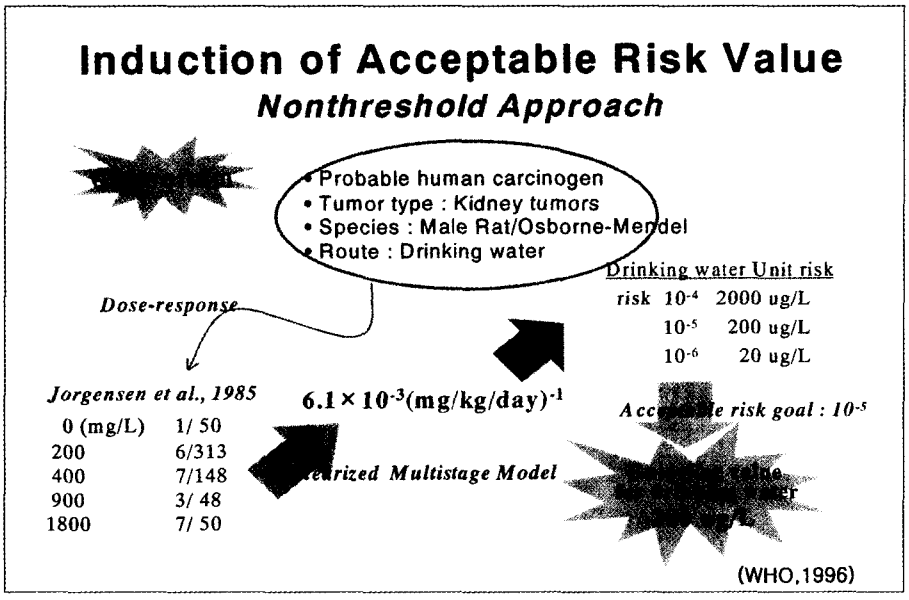

Fig. 3. Application of risk assessment for carcinogen in regulatory aspect

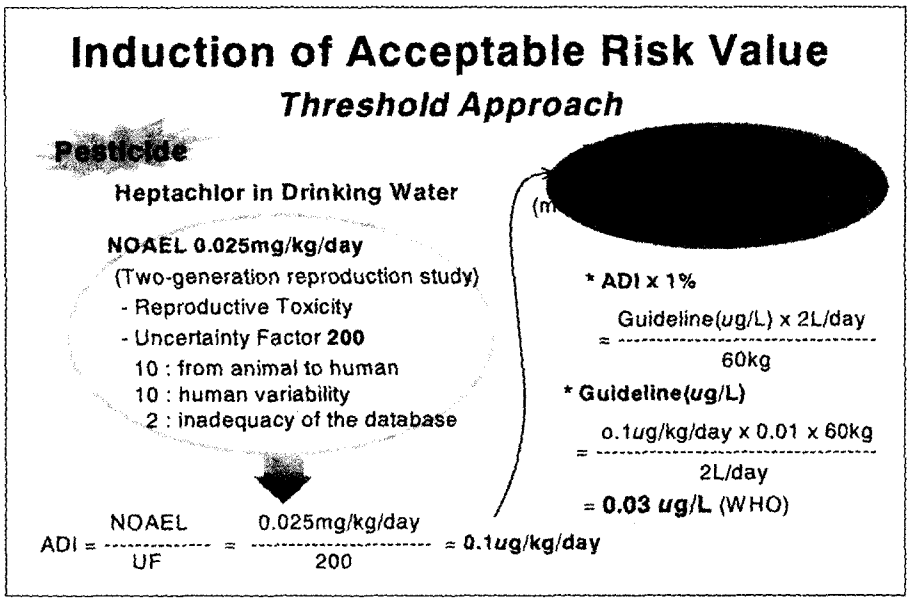

Fig. 4. Application of risk assessment for noncarcinogen in regulatory aspect.

Toxicity criteria data and exposure parameters are used to calculate the concentration of the chemicals of concern that correspond to a target risk level.

Figure 4 shows application example of risk assessment result using threshold approach for noncarcinogen in drinking water guideline suggested by WHO (1996).

By the Fig. 4, WHO has considered exposure contribution of heptachlor to drinking water as 1% of the ADI. because the main source of exposure seems be food, the guideline value is regulation.

IV. RISK MANAGEMENT AND REGULATION

Regulation demands have provided a major impetus for improvements in toxicological methods and they have stimulated a demand for major toxicological studies.

At least two issues must be resolved to justify government action to regulate human exposure to a substance. First, it must be determined that the substance is capable of harming persons who may be exposed. Second, it must be determined that could be harmful. In the absence of affirmative answers to both questions, government intervention to control exposure would be difficult to justify. A few statutes require only these two findings. Most laws under which chemicals are regulated, however, mandate or permit consideration of other criteria as well, such as the *magnitude* of the risk posed by a substance and the *consequences* of regulating it.

For the suggestion of regulatory option having safety against some chemical exposure, several issues must be considered as following.

- Regulation must be based on result of "plausible estimation" having real risk information.
- Risk assessment must identify total human exposure through multimedia as air, water, soil and food.
- The total exposure must be compared with safe level regarding long-term exposure.
- Risk management must consider economic, social and technical status.

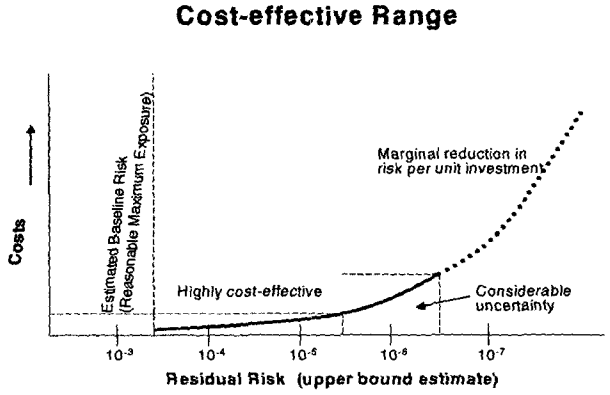

Fig. 5. Risk reduction versus costs.

Generally, a decision is made based on the alternative that accomplishes the desired objectives at the least total cost. Comparison between risks, and costs for various corrective action strategies is a necessary part of an overall risk management program.

Figure 5 shows that some managing option should be scientifically supportable and an optimal balance sought between risks and costs of risk reduction. If the risk to the some chemical is somewhat increase, the potential total cost can be reduced.

The finding of optimal combination point between risk and cost is very important in regulatory aspect.

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