

**GUIDELINES for INITIAL RISK  
ASSESSMENT of CHEMICAL SUBSTANCES  
(SUMMARY)**

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<<Note on translation>>

“Initial Risk Assessment Reports for Chemical Substances” were created by the National Institute of Technology and Evaluation (NITE) in collaboration with the Chemicals Evaluation and Research Institute, Japan (CERI) under the sponsorship of the New Energy and Industrial Technology Development Organization (NEDO).

This document is a summary of the “Guidelines for Initial Risk Assessment of Chemical Substances Version 2.0” (Japanese version) released in 2007.

## 1. Introduction

The Johannesburg Plan of Implementation of the World Summit on Sustainable Development (WSSD) (2002) included a commitment to aim

“To achieve, by 2020, that chemicals are used and produced in ways that lead to the minimization of significant adverse effects on human health and the environment, using transparent science-based risk assessment procedures and science-based risk management procedures, taking into account the precautionary approach as set out in principle 15 of the Rio Declaration on Environment and Development...”

In Japan, a project entitled “Risk Assessment and Development of Methods for the Risk Assessment of Chemical Substances,” funded by the New Energy and Industrial Technology Development Organization (NEDO), was started in 2001. Through this project, risk assessment methods for chemical substances in the environment were developed, and the series, “Initial Risk Assessment Reports for Chemical Substances” was published. This series of reports covers 150 substances. The reports were created by the National Institute of Technology and Evaluation (NITE) and the Chemicals Evaluation and Research Institute, Japan (CERI).

## 2. Exposure Assessment

### 2.1 Outline

In the environmental risk assessment, concentrations of chemical substances in the aquatic environment inhabited by organisms are estimated.

In the human health risk assessment, intake via two exposure pathways (oral and inhalation) is estimated. The estimation procedures are as follows:

Effects of complex exposure from multiple substances are not considered in this risk assessment.

- (1) *Measured* concentrations of the substance in the environment (air, river water, sea water, etc.), drinking water and food are collected.
- (2) Concentrations in air and river water are estimated by using mathematical models.
- (3) *Measured* concentrations are compared with the concentrations *estimated* by models. The higher value is selected to derive human intake and concentrations of a substance in the environment.

## 2.2 Collecting Monitoring Data

- 1) Measured concentrations in the environment, drinking water and food are collected from studies and other materials published by public agencies and institutions.
- 2) Collected data are examined concerning sampling points, sampling times and seasons, analysis methods, measurement frequency and number of samples, and then carefully evaluated for their reliability.
- 3) The ninety-fifth percentile values of the measured concentrations in air, in the aquatic environment (river, sea and ground water) and food are calculated respectively to use as “representative *measured* concentrations” for the risk assessment. In this statistical procedure, data which are less than their respective detection limits are replaced with a value equal to one half of the detection limit.
- 4) Regarding measured concentrations in tap water, the “representative *measured* concentration” is determined from the most recent data on annual-average substance concentrations measured at several measuring points. The highest concentration is selected as a “representative *measured* concentration” for the risk assessment.

## 2.3 Estimation of Environmental Concentrations by Mathematical Model

- 1) Estimation of concentrations in air

The estimation is conducted as follows:

- The land area of Japan is divided into 5km-mesh compartments.
- Concentrations in each 5km-mesh compartment are calculated using the AIST-ADMER<sup>1)</sup> with annual PRTR emission data as input.
- The highest concentration is selected as a concentration estimated by mathematical model (hereafter “representative *estimated* concentration”).

- 2) Estimation of concentrations in river water

Rivers have been selected as the representative aquatic environment for obtaining the *estimated* environmental concentration (EEC).

Concentrations are calculated using “IRM1”<sup>2)</sup> or “IAS”<sup>3)</sup> with annual PRTR emission data as input.

- (1) IRM1: When the release of a substance into the Kanto region accounts for a large portion of

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<sup>1)</sup> AIST-ADMER : “Atmospheric Dispersion Model for Exposure and Risk Assessment” developed by the National Institute of Advanced Industrial Science and Technology (AIST).  
[http://www.aist-riss.jp/software/admer/en/index\\_e.html](http://www.aist-riss.jp/software/admer/en/index_e.html)

<sup>2)</sup> IRM1: “Integrated River Model to predict the distribution of chemical concentration ver.1” developed by the Chemicals Evaluation and Research Institute, Japan (CERI)

<sup>3)</sup> IAS: “Initial Assessment System for the PRTR chemicals”, developed by the Japan Chemical Industry Association.

the total release in Japan, the maximum concentration estimated by IRM1 is used as a “representative *estimated* concentration.”

(2) IAS: In other cases, concentrations are estimated as follows:

- A business institution which releases the maximum amount of the substance is selected.
- A river where the business institution releases waste water is selected for further analysis.
- The concentration is estimated by using the amount of released and the stream flow of the river. This concentration is selected as a “representative *estimated* concentration”.

## **2.4 Determining Concentrations for Exposure Assessment**

The “representative *measured* concentrations” are compared with the “representative *estimated* concentrations” in each environmental compartment and the higher one is selected in each case to derive human intake and environmental exposure.

### 1) Air

- (1) The “representative *measured* concentration” is compared with the “representative *estimated* concentration,” and the higher one is selected for the exposure assessment.
- (2) In cases where both outdoor and indoor measured concentrations are available, the higher one is selected as the “representative *measured* concentration.”

### 2) Water (aquatic environment)

- (1) Rivers have been selected as the representative water compartment for obtaining the estimated environmental concentration (EEC).
- (2) The “representative *measured* concentration” is compared with the “representative *estimated* concentration,” and the higher one is selected for the exposure assessment.

### 3) Drinking water

- (1) Tap water data, measured by public agencies, are used, whenever possible, to derive the “representative *measured* concentration.”
- (2) When tap water data are not available, ground water data are used.
- (3) When neither tap water data nor ground water data are available, river water data are used to derive a “representative *measured* concentration”. The “representative *measured* concentration” is compared with the “representative *estimated* concentration,” and the higher one is selected to derive an estimated concentration in drinking water for the exposure assessment.

### 4) Food

- (1) Dietary intake of a substance or measured concentrations in food are used ,whenever possible,

to derive the “representative *measured* concentration.”

- (2) When such data are not available, data of concentrations in fish are used instead.
- (3) When neither food data nor fish data are available, a concentration in fish is estimated using the substance concentration in sea water and a bioconcentration factor (BCF) of fish as follows.

$$\boxed{\text{Estimated concentration in fish (mg/g)} = \text{Concentration in sea water (mg/L)} \times \text{BCF}}$$

If concentration in sea water is not available, it is assumed as 1/10 of representative concentration of rivers.

## 2.5 Estimated Environmental Concentrations for Environmental Risk Assessment

The environmental risk assessment is conducted for the effects on aquatic organisms. The estimated environmental concentration (EEC), used for the following risk characterization, is determined by procedures described in 2.4 2).

## 2.6 Estimation of Human Intake

In exposure assessment for human health, inhalation exposure via air and oral intake via food and drinking water are calculated. Exposure via other routes is considered when necessary.

### 1) Inhalation exposure

The inhalation rate is assumed to be 20 m<sup>3</sup>/day per person.

The intake of a substance is a product of the inhalation rate (20 m<sup>3</sup>/day) and the concentration in air described in 2.4.1). The absorption ratio of human body is assumed to be one (100%), except when absorption data of the substance are available for both humans and experimental animals. The average Japanese adult human body weight is assumed to be 50kg.

(Example)

Concentration in air: 0.2 µg/m<sup>3</sup>

$$\begin{aligned} \text{Exposure via inhalation route per body-weight: } & (0.2\mu\text{g}/\text{m}^3 \times 20 \text{ m}^3/\text{day}) / 50\text{kgBW}^4 \\ & = 0.08\mu\text{g}/\text{kgBW}/\text{day} \end{aligned}$$

### 2) Oral exposure

#### (1) Intake via drinking water

Intake rate of drinking water is assumed to be 2L /day per person. The intake of a substance is a product of intake rate (2L /day) and the concentrations described in 2.4.3).

#### (2) Intake via food

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<sup>4)</sup> BW: body weight

Intake rate of food is assumed to be 2,000g /day per person. The intake of a substance is a product of intake rate (2,000g / day) and the concentrations in food.

When no data on concentrations in food are available, concentrations in fish are used instead. In this case, assuming the intake of fish is 120g/day per Japanese person, the intake of a substance is estimated as the product of fish intake (120g/day) and the concentrations described in 2.4.4).

(Example-1)

Concentration in drinking water: 3µg/L

Concentration in food: 0.04µg/g

$$\begin{aligned} \text{Total intake via oral exposure: } & [(3\mu\text{g/L} \times 2\text{L/day}) + (0.04\mu\text{g/g} \times 2000\text{g/day})] / 50\text{kgBW} \\ & = 1.72\mu\text{g/kgBW/day} \end{aligned}$$

(Example-2)

Concentration in drinking water: 6µg/L

Concentration in food: No data

Concentration in fish: 0.8µg/g

$$\begin{aligned} \text{Total intake via oral exposure: } & [(6\mu\text{g/L} \times 2\text{L/day}) + (0.8\mu\text{g/g} \times 120\text{g/day})] / 50\text{kgBW} \\ & = 2.16\mu\text{g/kgBW/day} \end{aligned}$$

### 3) Exposure via consumer products

When exposure via consumer products is of concern and reliable data for risk assessment of the exposure are available, exposure via consumer products is also calculated.

## 3. Hazard Assessment

### 3.1 Collecting and Evaluating Hazard Information

- 1) Hazard information of a substance is collected from academic literature or toxicity documents and assessment reports published by international or governmental organizations.
- 2) The collected information is carefully evaluated for its adequacy and reliability for risk assessment by confirming the followings:
  - a) Information about tested chemicals and organisms/animals is clear and definite.
  - b) Study protocols are described distinctly.
  - c) Tests are performed based on authorized test guidelines.
  - d) Judgment criteria are clear and definite (e.g. description of statistical analysis).
  - e) Studies were quoted in assessment documents that have a review system.
  - f) Studies have appeared in journals that have a review system.

- g) Tests are performed under Good Laboratory Practice (GLP) principles.
- 3) Nondisclosure documents, (e.g., internal data of business corporations), are not considered reliable because their details are not open for evaluation. However, if international institutes have quoted such data for their assessments, the data is considered reliable and can be used for risk assessments.

### **3.2 Effects on Organisms in the Environment**

The environmental risk characterization is conducted, in principle, using chronic toxicity data of the representative aquatic lives of three trophic levels in the food-chain, that is, algae, invertebrates and fish.

- 1) Hazard data of algae, invertebrates, and fish are collected.
- 2) Reliability and adequacy of the collected data are evaluated based on the criteria described in 3.1.2)

- 3) Toxicity to algae

In principle, the 72 or 96 hour NOEC is used as the chronic toxicity for the risk assessment. In cases where the NOEC is not available, a 72 or 96 hour EC<sub>10</sub> is substituted for the NOEC. If a growth inhibition test is used to derive the NOEC, it is necessary to distinguish whether the data was derived by measuring biomass, or whether it was derived from growth rate by measuring the number of cells. If both data are available, growth rate data is used.

- 4) Toxicity to invertebrates

Crustacea have been selected as the representative invertebrates for the assessment.

- 5) Toxicity to fish

Toxicity data on freshwater fish and sea fish are selected.

The chronic toxicity for the risk assessment is derived from 21-day, or longer, NOECs. In addition, early-life stage tests on fish, which start by placing fertilized eggs in test chambers and continue at least until all the control fish are free-feeding, are treated the same as chronic toxicity.

- 6) A study in which a surface-active dispersant is used is generally not used for risk assessments. However, if no other data available, the data may be used with careful evaluation of the effects of the surface-active dispersant on the test results. In this case, use of a surface-active dispersant should be described in the risk assessment report.

### **3.3 Effects on Human Health**

- 1) The reliability and adequacy of the collected data are evaluated based on the methods and conditions of the experiment, compliance with authorized guidelines, conformity to Good Laboratory Practice (GLP) principles and information about analogue substances, if available. Any data selected for the risk assessment must be determined to be adequate and reliable based on

this comprehensive evaluation.

- 2) A NOAEL derived from an experiment in which a LOAEL was not derived is not considered appropriate for use of the risk assessment. In this case, consistency with other experimental data (e.g., the presence of an outlier) should be evaluated carefully.

### **3.3.1 Epidemiological Studies**

An epidemiological study is apt to be affected by confounding factors as well as multiple substance exposure. Thus, it is necessary to more carefully evaluate the reliability of an epidemiological study than experimental animal studies.

### **3.3.2 Toxicity Studies Using Experimental Animals**

- 1) Repeated dose toxicity

The severity of effects, dose-response relations, time-response relations and reversibility of the adverse effect of a substance are evaluated. Then the NOAEL (or LOAEL) is selected for the risk assessment.

- 2) Reproductive and developmental toxicity

It is necessary to distinguish, to the extent possible, between specific effects caused by the reproductive/developmental toxicity of a substance and non-specific reproductive adverse effects caused by general repeated toxicity (e.g., decrease in water or food consumption and stress on maternal animal).

- 3) Genotoxicity

Possibility that a substance is a genotoxic carcinogen or is genotoxic to humans is closely examined. It is important to determine the potential of a substance to damage genetic material in a reproductive cell and determine the toxicity to the development of a somatic cell.

- 4) Carcinogenicity

Since a carcinogenic substance having no genotoxicity is considered to have a toxic threshold, a NOAEL of the substance are derived from carcinogenicity tests, if possible. Evaluation by international institutes (e.g. IARC<sup>5)</sup> monographs) are shown as well.

## **4. Risk Characterization Procedures**

### **4.1 Environmental Risk Characterization**

- 1) The environmental risk assessment is conducted using aquatic organisms. Toxicity is evaluated for aquatic lives representative of three trophic levels in the food chain, that is, algae, crustacea and fish. Classification and end-points (critical effects) are shown in Table 1.

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<sup>5)</sup> IARC: International Agency for Research on Cancer

**Table 1 Toxicity on organisms in the environment**

Aquatic organisms	Chronic toxicity		Acute toxicity	
Algae	72 or 96 hour NOEC(or EC <sub>10</sub> )	Growth inhibition (growth rate or biomass)	72 or 96 hour EC <sub>50</sub>	Growth inhibition (growth rate or biomass)
Crustacea	7 day or longer NOEC	Mortality, Reproduction, Growth	24 or 48 hour EC <sub>50</sub> or LC <sub>50</sub>	Immobilization, Mortality
Fish	21 day or longer NOEC, LOEC or LC <sub>50</sub>	Mortality, Reproduction, Growth, Development (serious malformation)	96 hour LC <sub>50</sub>	Mortality

- 2) Minimum values from chronic toxicity tests for each of the three trophic levels are used to determine species for use in the “key-studies.” When no reliable chronic toxicity data is available, or the value of acute toxicity is lower than that of chronic toxicity, the value of acute toxicity is used for the risk characterization.
- 3) Chronic toxicity data from field tests on the 3 species (algae, crustacea and fish) should be used whenever possible. However, if toxicity information on the substance being assessed is incomplete, uncertainty factor (UF) are used for extrapolation.

**Table 2 Uncertainty factors for environmental risk assessments**

Elements of extrapolation	Default UF
<b>Laboratory test to field test</b>	
- Extrapolation from laboratory test to field test	10
<b>Acute to chronic</b>	
- Chronic toxicity data on two species, representing two trophic levels, are available	5
- Chronic toxicity data on one species, representing one nutritional stage are available	10
- Only acute toxicity data are available, (except the case mentioned below).	100

- Only acute toxicity data are available, including acute toxicity data for algae, crustacea, fish and many species, including the most sensitive species (e.g., water flea or shrimp) are available. 10

**Using of LOEL, EC<sub>50</sub>, LC<sub>50</sub> and others**

- When a value other than the NOEC (i.e., LOEC, EC<sub>50</sub>, LC<sub>50</sub>) is used as the chronic toxicity data 2

**Additional factor**

- Based on the quality and method of the experiment, an assessor may add an additional factor, in particular cases. --
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- 4) The product of uncertainty factor (UF) is calculated by multiplying the appropriate default uncertainty factors shown in Table 2.

(Example)

Chronic toxicity data (LOEC) on crustacea and acute data on algae and fish are selected for risk assessment;

Product of Uncertainty Factor (UF) = Extrapolation from laboratory test to field test (10) × Chronic toxicity data of one species (10) × Using of LOEC (2) = 200

- 5) The margin of exposure (MOE) is calculated as follows:

$$\boxed{MOE = NOEC / EEC}$$

- 6) Comparing the MOE with the UF, risk to organisms in the environment is characterized as shown in Table 5.

**4.2 Human Health Risk Characterization**

- 1) When reliable toxicity data for both humans and experimental animals are available, the human toxicity data is used for the human health risk characterization. When no reliable studies on human toxicity are available, studies with experimental animals are used with careful consideration for species differences between humans and the test animals.

- 2) In the Initial Risk Assessment, the risk characterization is based primarily on the general repeated dose toxicity. The NOAEL (or LOAEL) for risk characterization is selected as follows:

(1) The minimum NOAEL (or LOAEL) among several repeated dose toxicity studies is selected in principle.

(2) Reproductive and developmental toxicities are evaluated. Where the value of the NOAEL for reproductive and developmental toxicity is smaller than the NOAEL for repeated dose toxicity, a risk characterization for reproductive and developmental toxicity is conducted.

(3) For a carcinogenic substance that is not considered to have genotoxicity, risk characterization on carcinogenicity is carried out with an available NOAEL, assuming that there is a toxic threshold. In other cases, risk assessment for carcinogenicity is not conducted.

3) The MOE is calculated as follows:

$$\text{MOE} = \text{NOAEL} / \text{Estimated Human Intake (EHI)}$$

The MOE is calculated for each exposure route (i.e., inhalation and oral).

4) When both intake via oral and via inhalation are available, but toxicity data is available for only one exposure route (inhalation or oral), the MOE may be calculated using total intake from both routes (inhalation and oral) and toxicity data of one route.

(Example) Oral intake: 0.04µg/kgBW/day  
 Inhalation intake: 0.01µg/kgBW/day  
 NOAEL<sub>oral</sub> : 2µg/kgBW/day,  
 NOAEL<sub>inhalation</sub>: Not available  
 Estimated Human Intake (total): 0.03+0.01 = 0.04µg/kgBW/day  
 used NOAEL: 2µg/kgBW/day  
 MOE<sub>total</sub> = 50

5) If the frequency of the dose or dosing duration of the experiment is not 7days in a week or 24 hours in a day, the NOAEL is converted to the value of 7days in a week and 24 hours in a day.

(Example) NOAEL (5day/ week, 8hours/ day) = 2µg/kgBW/day  
 Converted NOAEL = 2µg/kg × 5 /7 × 8/ 24 = 0.48µg/kgBW/day

6) In inhalation experiments, an NOAEL derived from experimental animal studies is converted by using the values below:

**Table 3 Inhalation rate and body weight for human, rat and mouse**

	Human	Rat	Mouse
Inhalation	20m <sup>3</sup> /day	0.26m <sup>3</sup> /day	0.05m <sup>3</sup> /day
Body weight (BW)	50kg	0.35kg	0.03kg

(Example) NOAEL: 3µg/m<sup>3</sup> for rat  
 Inhalation rate of rat: 0.26m<sup>3</sup>/day  
 Body weight of rat: 0.35kg  
 Converted NOAEL = 3µg/m<sup>3</sup> × 0.26 m<sup>3</sup>/day /0.35kg = 2.22µg /kgBW /day

8) The uncertainty factors for human health risk assessments, shown in Table 4, are in conformity

with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1998.

**Table 4 Uncertainty factors for human health risk assessments**

Elements of extrapolation	Default UF
- Interspecies (extrapolation from animal to human)	10
- Intraspecies (intraspecies difference, individual difference)	10
- Using LOAEL	10
- Duration of test	
1 month or longer	10
3 months or longer	5
6 months or longer	2
12 months or longer	1
- Carcinogenicity	10
(Additional factor)	
Based on the quality and method of the experiment, an assessor may deem it necessary to use the additional factor, in particular cases.	

8) The product of uncertainty factor is calculated by multiplying the appropriate uncertainty factors shown above.

(Example)

In the case of a 6-month experiment with a mouse

Product of uncertainty factor (UF) = Interspecies difference (10) × Intraspecies difference (10) × Duration of test (2) = 200

9) Risk to human health is characterized by comparing the MOE with the product of uncertainty factor (UF). Refer to Table 2.

10) When the UF is over 10,000, a risk characterization is not conducted because the reliability of the toxicity data is considered insufficient.

## 5. Risk Assessment of Inorganic Substances, Metals and Metal Compounds

Under the PRTR law, inorganic substances, metals and metal compounds are defined respectively (e.g., zinc is designated as “zinc compounds (water-soluble)”; arsenic is defined as “arsenic and its inorganic compounds”). The Initial Risk Assessments were carried out based on these definitions. Inorganic substances, metals and metal compounds exist in various forms, and can change their

chemical species in the environment. These chemical species have different hazardous properties. However, only few measured environmental concentrations are available for each species. Taking that into consideration, the risk assessments for these substances are carried out as follows:

1) Selecting chemicals for risk assessment

Chemicals are selected based on quantity of domestic production and import, uses, and adverse effects on human health and organisms in the environment.

2) Hazard assessment

The NOAEL or NOEC values of these chemicals are evaluated, and selected values are used for the risk assessment. These selected values are then converted into NOAEL or NOEC values based on the pure (elemental) form of the inorganic substance or metal.

3) Exposure assessment

Despite the fact that inorganic substances, metals and metal compounds change chemical species in the environment, most of the measured concentrations in the environment are total concentrations of pure (elemental) forms of the inorganic substances, metals and metal compounds. Therefore estimated environmental concentrations (EEC) and estimated human intake are derived as total concentrations of pure (elemental) forms of the inorganic substances, metals and metal compounds. These concentrations are considered to include exposure from natural sources.

4) Risk characterization

The minimum value of multiple NOECs or NOAELs of “typical chemicals” is selected for the risk characterization. The margin of exposure (MOE) is calculated as described in 4.1 and 4.2. The risk characterization is conducted by comparing the MOE with the product of uncertainty factor (UF).

5) Essential metal elements

In cases where the substance is an essential element for the human body, the Tolerable Upper Intake Level, specified in Dietary Reference Intakes issued by the Ministry of Health, Labor and Welfare in Japan, is used as the NOAEL. In this case, the uncertainty factor is considered one.

6) Estimation by mathematical model

Estimation of environmental concentrations by mathematical model is not performed, because it is difficult to estimate environmental concentrations due to natural generation, occurrence, and transport between environmental compartments.

**Table 5 Risk characterizations from Initial Risk Assessments**

Comparison between MOE and the product of uncertainty factor (UF)	Product of uncertainty factor (UF)		
	UF ≤ 10	10 < UF ≤ 100	100 < UF ≤ 1,000 (for environmental) 100 < UF ≤ 10,000 (for human health)
MOE ≤ UF	The substance is considered to be of concern and given higher priority for further investigation, analysis and assessment.	The substance is considered to be of concern. Further investigation, analysis and assessment are necessary.	The substance is considered to be of concern. Further investigation and assessment of toxicity studies is necessary.
MOE > UF	The substance is considered to be of no immediate concern and a low priority for further work		
Impossible to derive MOE	It is necessary to collect missing data (on hazards or exposure).		

## **Appendix**

The Initial Risk Assessments were initially conducted based on Guideline Ver.1.0. The Guideline was subsequently revised to Guideline Ver.2.0. This document is based on Guideline ver.2.0.

One of the main areas of the revision is in the determination of estimated environmental concentrations for the exposure assessment.

### **Ver.1.0**

When adequate measured concentrations issued by public institutes are available, the data are used for the exposure assessment (without comparison to values estimated by mathematical model).

### **Ver.2.0**

When adequate measured concentrations issued by public institutes are available, *measured* concentrations are compared with *estimated* concentrations, calculated by mathematical model, and the higher value is selected for the exposure assessment.