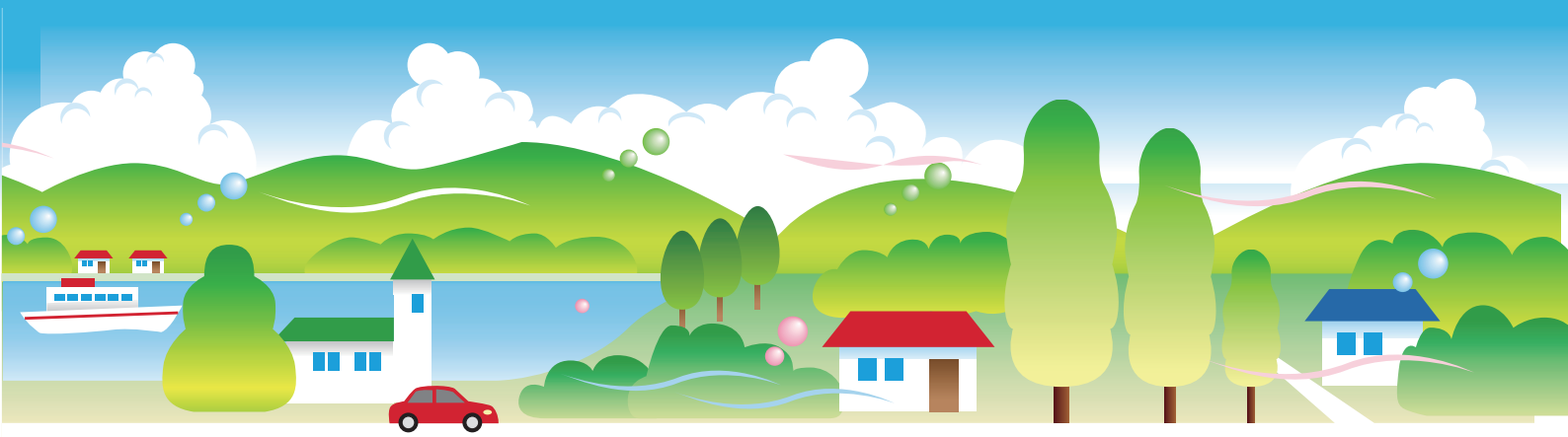
Risk Assessment on Chemicals

For Better Understanding



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Incorporated Administrative Agency
National Institute of Technology and Evaluation
Chemical Management Center

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Introduction

The risks of chemicals are determined by hazards and exposures.*1

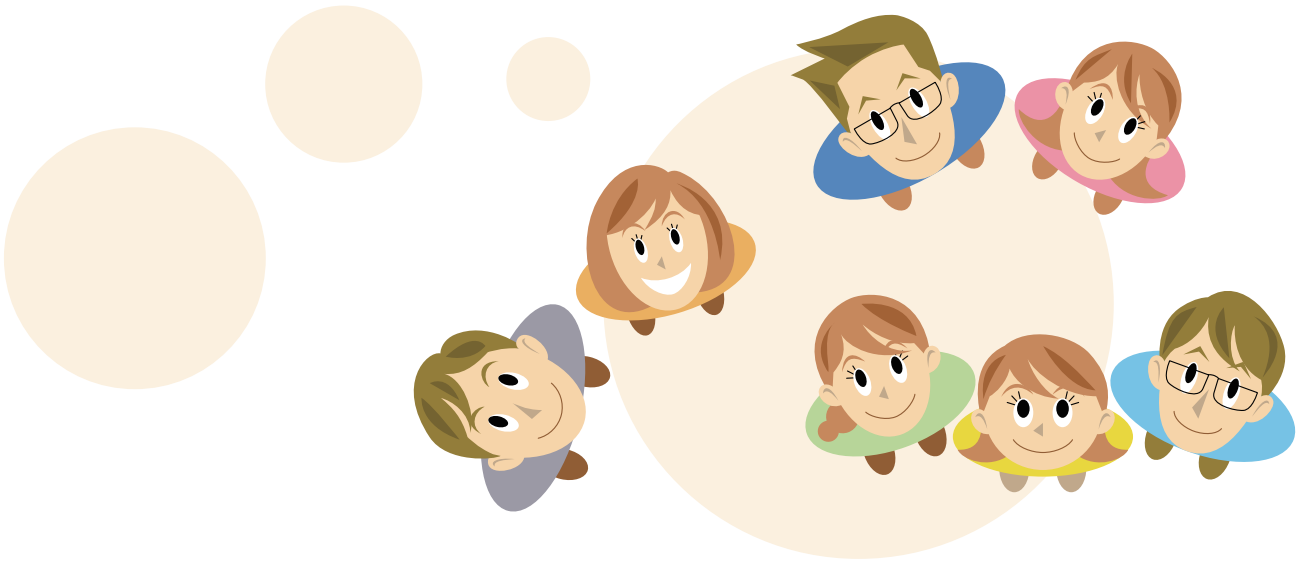
*1: Exposures: Being exposed to substances (a general term for inhalation, ingestion, touching)

Risk = Hazards × Exposures

Therefore, when we consider risk management of chemicals, it is essential not only to evaluate the hazards of individual chemicals but also to assess the risk of chemicals through combining hazards with exposures and to conduct risk management based on such assessment results.

The results and data from risk assessments serve as important materials for appropriate risk management of chemicals (judging the acceptability of the risk, considering the necessity of risk reduction etc. and risk communication (sharing information and exchanging opinions and making discussions about risks among stakeholders, such as the government, enterprises and citizens, to establish common recognition and trustful relationships).

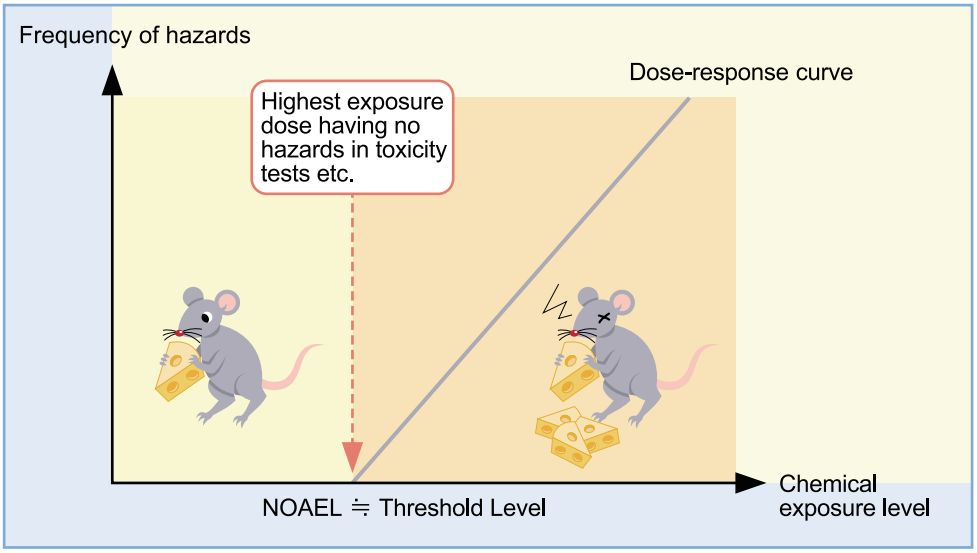
*This document is a brief guide to Risk Assessment for human health.
Risk Assessment of chemicals is roughly divided into “human health” and “ecotoxicity.”
Risk Assessment of chemicals additionally aims to assess “physical risk” arising from accidents such as explosion and fire.



Concepts of Risk Assessment

The highest exposure dose having no hazards (called the "threshold level"[*1]) can be determined from the evaluation of hazards in toxicity tests etc.
Risk Assessment of chemicals is conducted by **comparing the magnitude of the "estimated exposures"** based on the threshold level and exposure evaluation.

*1: See p. 8 (Methods and threshold levels for carcinogenicity assessment)

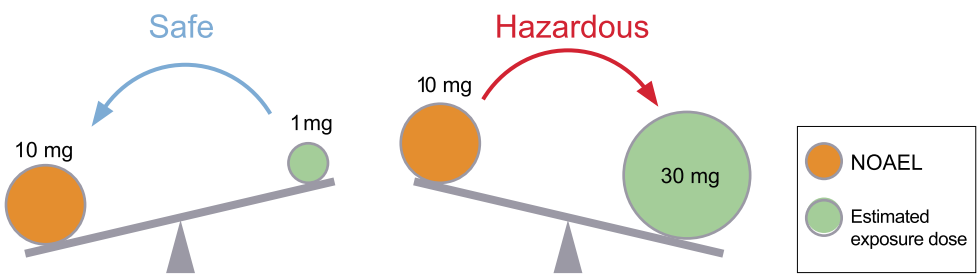


If the highest exposure dose having no hazards is the No Observed Adverse Effect Level (NOAEL), which is approximately equal (≒) to the threshold level, there will be no hazards when the estimated exposure dose is lower than the NOAEL. One such example is:

NOAEL	10 mg/kg/day
Estimated exposure dose	1 mg/kg/day

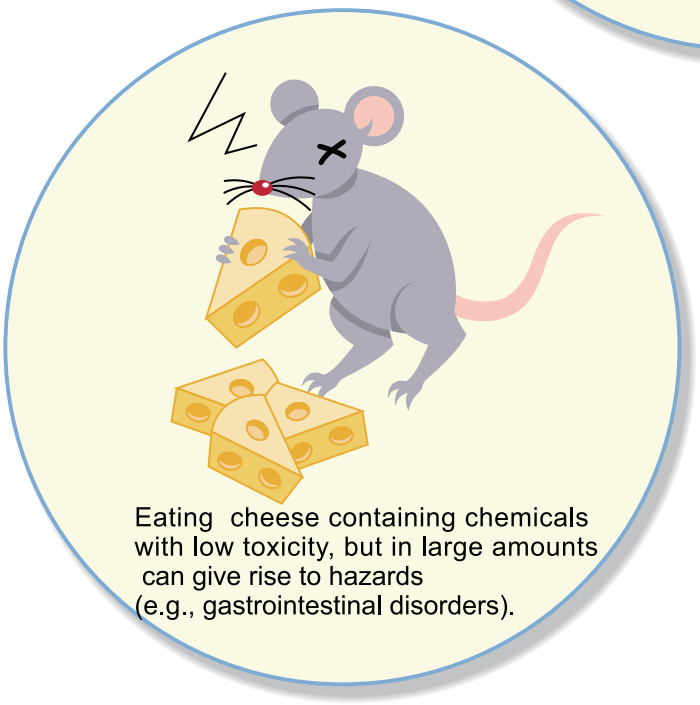
If the estimated exposure dose is higher than the NOAEL, hazards may appear. One such example is:

NOAEL	10 mg/kg/day
Estimated exposure dose	30 mg/kg/day



When a chemical has high toxicity (low NOAEL), no hazards appear if the exposure is lower than the NOAEL. Conversely, if a chemical has low toxicity (high NOAEL), hazards may appear if the exposure is higher than the NOAEL.
This is the concept of “Risk Asessment.”

Eating cheese containing highly toxic chemicals does not give rise to hazards if the amount taken is small.



Eating cheese containing chemicals with low toxicity, but in large amounts can give rise to hazards (e.g., gastrointestinal disorders).

Risk Assessment Methods

Risk assessment generally uses factors such as HQ (Hazard Quotient) and MOE (Margin Of Exposure). Both factors are based on the same concepts.

Risk Assessment HQ

HQ (Hazard Quotient) is calculated according to the following equation:

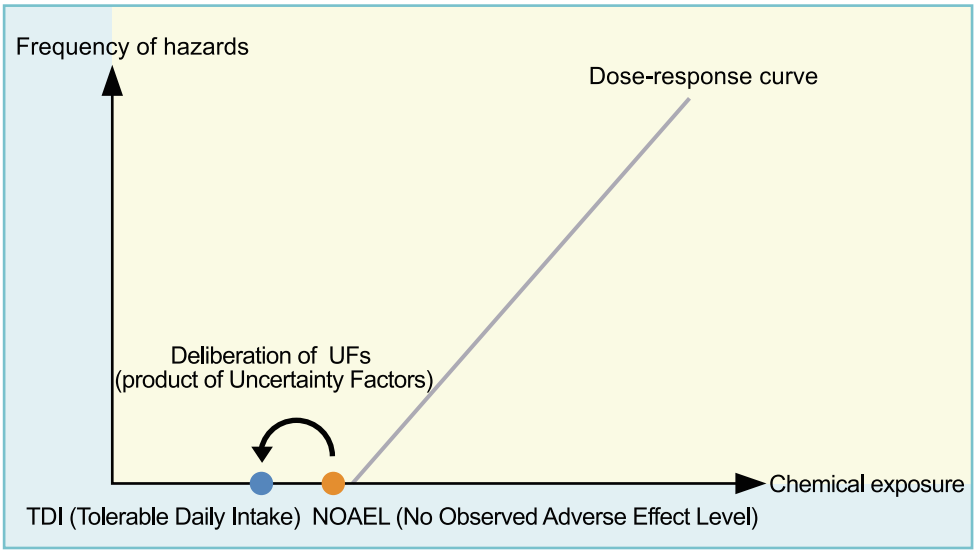
$$\text{HQ (Hazard Quotient)} = \frac{\text{EHE (Estimated Human Exposure)}}{\text{TDI (Tolerable Daily Intake)}}$$

TDI (Tolerable Daily Intake)[*1] is the amount of a chemical that can be taken daily by humans in a safe manner. It is calculated by dividing the NOAEL (No Observed Adverse Effect Level, determined in toxicity tests, etc.) by UFs (product of Uncertainty Factors)[*2] and converted to the NOAEL for humans.

*1: See p. 6 “NOAEL (No Observed Adverse Effect Level) and TDI (Tolerable Daily Intake)”

*2: See p. 12 “UF (Uncertainty Factor)”

$$\text{TDI (Tolerable Daily Intake)} = \frac{\text{NOAEL (No Observed Adverse Effect Level)}}{\text{UFs (product of Uncertainty Factors)}}$$



HQ (Hazard Quotient) compares the magnitude of EHE (Estimated Human Exposure)[*3] with that of TDI (Tolerable Daily Intake). If HQ is larger than 1, i.e., if EHE exceeds TDI, there is risk. If HQ is smaller than 1, i.e., if EHE does not exceed TDI, there is no risk.

*3: See p. 10 “EHE (Estimated Human Exposure)”

If HQ (Hazard Quotient) ≥ 1	**Risk**
If HQ (Hazard Quotient) < 1	**No Risk**

Risk Assessment using MOE (Margin Of Exposure)

MOE (Margin Of Exposure) is calculated according to the following equation:

$$\text{MOE (Margin Of Exposure)} = \frac{\text{NOAEL (No Observed Adverse Effect Level)}}{\text{EHE (Estimated Human Exposure)}}$$

MOE (Margin Of Exposure) compares the magnitude of NOAEL (No Observed Adverse Effect Level) with that of EHE (Estimated Human Exposure). However the NOAEL is determined by toxicity tests, etc., so the calculation of MOE does not incorporate conversion into humans (it does not take uncertainty into consideration). So, MOE needs to be **compared with UFs (product of Uncertainty Factors).** If MOE is smaller than UFs, there is risk. If MOE is larger than UFs, there is no risk.

If MOE (Margin Of Exposure) ≤ UFs (product of Uncertainty Factors)	**Risk**
If MOE (Margin Of Exposure) > UFs (product of Uncertainty Factors)	**No Risk**

We may say that larger the UFs (product of Uncertainty Factors) are, the less reliable the assessment results become.

Differences in Risk Assessment methods

HQ (Hazard Quotient) includes UFs (product of Uncertainty Factors). So, whether or not the HQ is larger than 1 can be used as evaluation standards for Risk Assessments. MOE (Margin Of Exposure), on the other hand, does not include UFs (product of Uncertainty Factors). So, whether or not MOE is larger than UFs can be used as evaluation standards for Risk Asessments.

HQ (Hazard Quotient) is advantageous in that whether or not there is risk can be simply determined only by checking whether HQ is lager or smaller than 1.
Unlike HQ, MOE (Margin Of Exposure) does not include UFs (product of Uncertainty Factors). MOE is advantageous in that it enables numerical analysis of uncertainty in Risk Assessment if used as a reference parameter, thus making differences by improving reliability, i.e., making it clear whether a judgment of "possible hazards" is attributable to a shortage of information (resulting in high UFs) or to the availability of information that is to some extent reliable.

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*Within the framework of "General Chemicals Evaluation and Control Program" under NEDO Project, "Initial Risk Assessment Report" is prepared, and information related to risk assessment on chemicals is supplied.
http://www.safe.nite.go.jp/english/risk/initial_risk.html

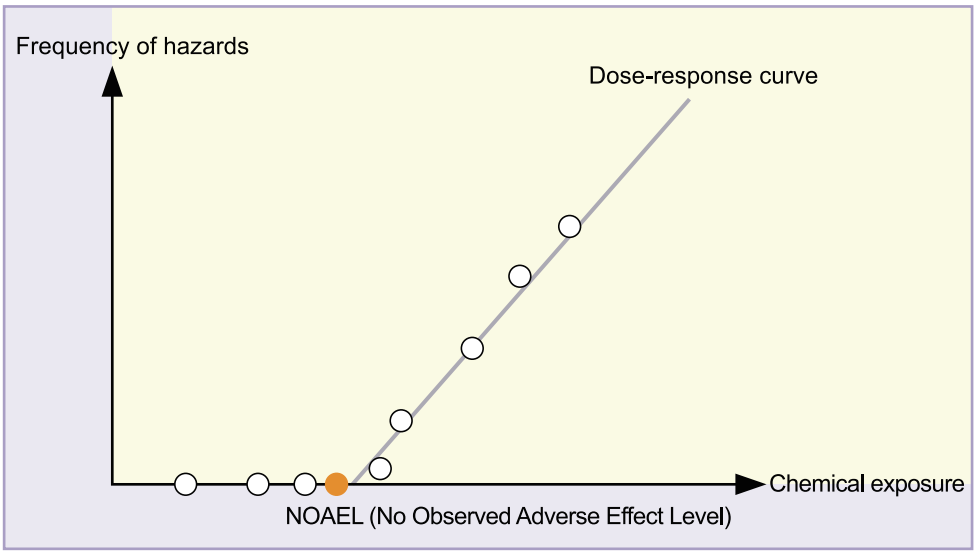
"Initial Risk Assessment Report" involves assessment of risks caused by chemicals in human health and ecotoxities and is prepared to determine the necessity of a more detailed risk assessment and the priority of chemicals requiring such assessments. Initial Risk Assessment used the MOE (Margin Of Exposure) as a factor.

*The explanation given above corresponds the influence on human health. When the influence on ecotoxicities is assessed, NOEC (No Observed Effect Concentration) instead of NOAEL (No Observed Adverse Effect Level), EEC (Estimated Environmental Concentration) rather than EHE (Estimated Human Exposure) is used.

NOAEL (No Observed Adverse Effect Level) and TDI (Tolerable Daily Intake)

What is NOAEL (No Observed Adverse Effect Level)?

The highest exposure of a chemical, determined in toxicity tests etc., having no adverse effect (e.g., onset of sickness) even when the chemical is taken (exposed) daily for the rest of one's life. In practice, mice, rats or other animals are forced to take a chemical for a certain period of time. This test is repeated several times at varying dose levels. The highest dose level causing no adverse effect in these tests is adopted as NOAEL (No Observed Adverse Effect Level). Usually, NOAEL is expressed in the amount of a chemical taken daily per kg body weight (e.g., mg/kg/day).



NOAEL is determined by the toxicity tests etc. listed below.

Long-term toxicity*1	Toxicity appearing following a long-term continued exposure (repeated exposure)
Reproductive and developmental toxicity	Toxicity exerting adverse effects on parent's reproductive function and fetuses
Carcinogenicity*2	Potential of causing cancer of various types
Respiratory tract irritation	Potential of causing respiratory tract allergies (asthma, etc.)

*1: Also called "repeated dose toxicity"

*2: In some cases there is no NOAEL for carcinogenicity.

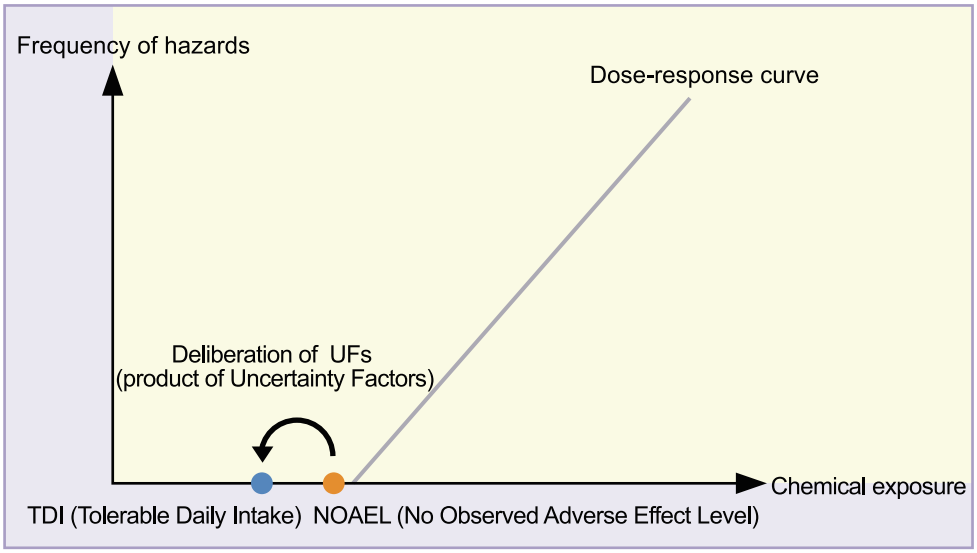
→ See p. 8 "Methods and threshold levels for carcinogenicity assessment"

What is TDI (Tolerable Daily Intake)?

The highest exposure of a chemical having no adverse effect (e.g., onset of sickness) on humans even when the chemical is taken (exposed) daily for the rest of one's life. NOAEL (No Observed Adverse Effect Level), determined by toxicity studies etc., is divided by UFs (product of Uncertainty Factors)*3 to convert it to human NOAEL. Usually, NOAEL is expressed in the amount of a chemical taken daily per kg body weight (e.g., mg/kg/day).

*3: See p. 12 "UF (Uncertainty Factor)"

$$\text{TDI (Tolerable Daily Intake)} = \frac{\text{NOAEL (No Observed Adverse Effect Level)}}{\text{UFs (product of Uncertainty Factors)}}$$



ADI (Acceptable Daily Intake) and RfD (Reference Dose) are also used as terms having the same meaning as TDI.

*"Initial Risk Assessment Report" of the NEDO Project achieved the NOAEL determined by a reference survey on long-term toxicity, reproductive and developmental toxicity, carcinogenicity and so on.
http://www.safe.nite.go.jp/english/risk/initial_risk.html

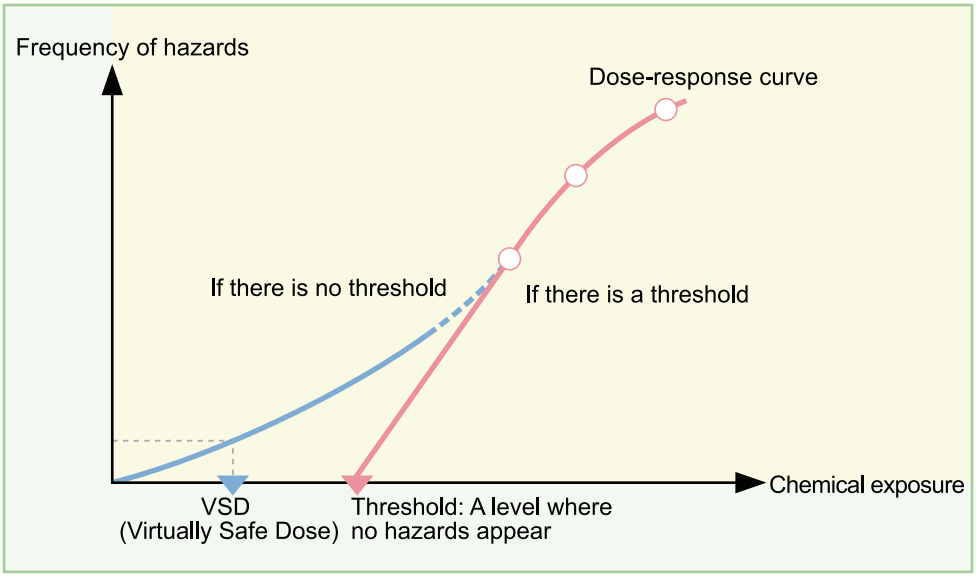
Related Terms

LOAEL (Lowest Observed Adverse Effect Level)
NOEC (No Observed Effect Concentration)
LOEC (Lowest Observed Effect Concentration)

Methods and Threshold Levels for Carcinogenicity Assessment

Unlike other non-cancerous symptoms, **when a carcinogen infiltrates a gene to create cancer cells,** there is no minimum level of carcinogen without the possibility of causing cancer, even **the lowest level of carcinogen is still considered to have a potential of causing cancer.**

The term "threshold" is used to indicate the amount of intake or the exposure of a chemical without a potential of adverse effects. If a chemical has the potential of exhibiting adverse effects unless the exposure level is zero (none), this chemical is considered as having "no threshold." Conversely, if a chemical has a minimum effective exposure level that does not exhibit adverse effects, the chemical is considered to have "a threshold".



If there is no threshold of hazards, there is no NOAEL (No Observed Adverse Effect Level) and also the TDI (Tolerable Daily Intake)*1, therefore the method for Risk Assessment differs from the method used for cases where there is NOAEL.

*1: See p. 6 "NOAEL (No Observed Adverse Effect Level) and TDI (Tolerable Daily Intake)"

One method of Risk Assessment used in such cases adopts "the amount causing carcinogenesis at a probability of 1/100,000" as VSD (Virtually Safe Dose), instead of adopting NOAEL or TDI.

Carcinogenicity through injury of genes and mutagenicity etc. through activity on germ cells are now considered to have no threshold.*2

*2: There are multiple opinions regarding threshold for carcinogenicity. This topic is still controversial.

*"Initial Risk Assessment Report" under the NEDO Project evaluates carcinogenicity as shown on the below website.
http://www.safe.nite.go.jp/english/risk/initial_risk.html

Carcinogens without gene injury (with threshold)

For these carcinogens, Risk Assessment with MOE (Margin Of Exposure) is carried out, similar to the method used for other types of toxicity.

The two factors, listed below, are additionally taken into account as uncertainty factors (UF).

- Carcinogenicity (× 1 to 10)
- Corresponding to seriousness related to cancer cell type, favorite site, expression etc. (× 1 to 10)

Carcinogens with gene injury (no threshold)

Because there is no threshold, risk assessment by MOE (Margin Of Exposure) is not possible. So, if quantitative evaluation by evaluation organizations such as EPA (Environment Protection Agency, USA) and WHO (World Health Organization) can be utilized, the unit risk etc. expressing the probability of carcinogenicity* is shown.

However, when final judgment is made, unit risk or the like serves only as reference information and is treated as "a candidate of substances needed for detailed Risk Assessment."

Footnote

*Unit risk: The upper limit of the predicted risk for carcinogenesis following daily exposure to a chemical at a concentration of 1 μg/L (water) or 1 μg/m^3 (air) throughout one's lifetime (70 years).

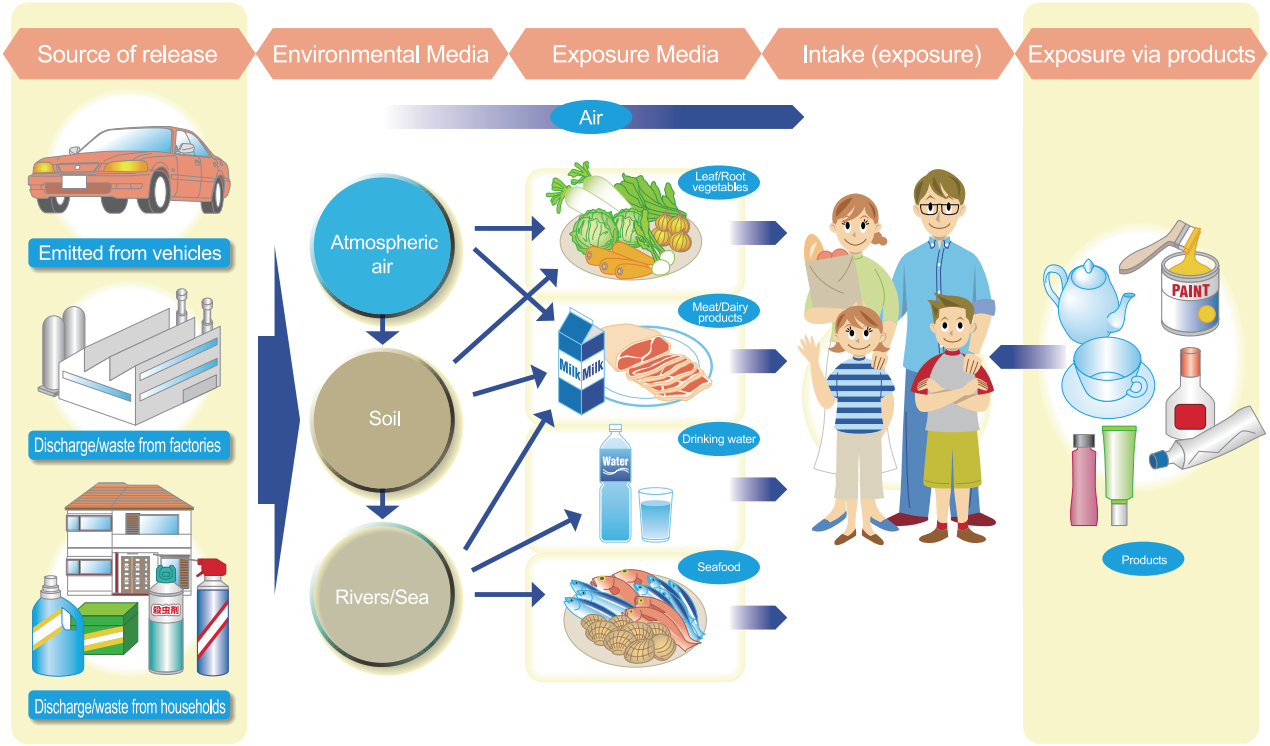
EHE (Estimated Human Exposure)

What is EHE?

EHE is the estimated exposures at which chemicals have effects on humans,, calculated on the basis of assumptions about respiration, amounts of meals, body weight and so on.

Exposure can be divided by route into “direct exposure” and “indirect exposure.”
“Direct exposure” for example, is a direct intake of chemicals while working etc. at a factory.

“Indirect exposure” means indirect intake of chemicals through their release ⇒ being discharged to the environment ⇒ breathing the air, drinking the water, eating the foods, etc. ⇒ and thus intaking them (exposure). It is also called “exposure via environment.”
*“Indirect exposure” sometimes occurs via products.

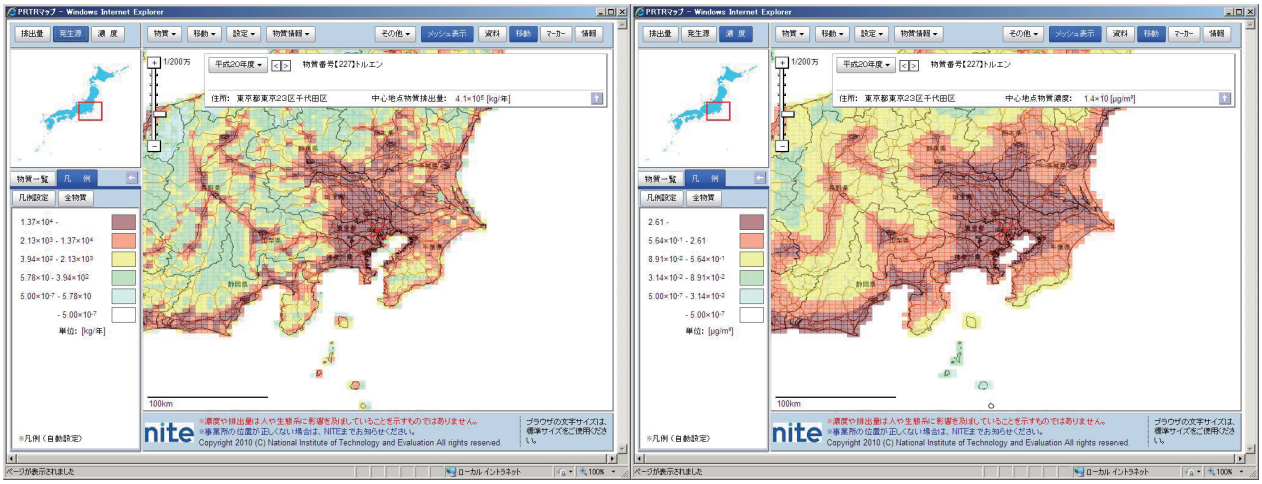


The practical exposure level for individuals varies depending on chemicals and the living environment (place of living, foods routinely ingested, and so on).
Not all the chemicals that are contained in the air, drinking water and foods are absorbed, and the absorbed chemical substances do not all affect humans and the living body.

The term “EHI” (Estimated Human Intake) is sometimes used in the same meaning as EHE.

*"Initial Risk Assessment Report" under the NEDO Project primarily shows estimates of indirect exposure.
http://www.safe.nite.go.jp/english/risk/initial_risk.html

EHE is obtained by calculating the monitoring data and data on PRTR emission for **an assumed case of maximum human exposure in Japan.**



Reference information: Map of Toluene sources (left) and Map of ambient Toluene concentrations
http://www.taikimap.nite.go.jp/prtr/top.do(Japanese only)

Methods for calculation of estimated total exposure at the time of Initial Risk Assessment

The amount of daily intake by five routes listed below are totaled and divided by the human body weight (50 kg) to yield Total Exposure Level in units of mg/kg/day or μg/kg/day.

1) **Exposure via respiration**
   Concentration in ambient air × amount of air inhaled (20 m^3/day) = exposures
2) **Exposure via drinking water**
   Concentration in drinking water × amount of water taken (2 L/head/day) = exposures
3) **Exposure via foods**
   Concentration in foods × amount of foods ingested = exposures
   If the data on concentration in foods are not available, exposures by intake of fish/shellfish is calculated.
   Concentration in fish/shellfish × amount of fish/shellfish ingested (120 g/day) = exposures
4) **Exposure via other foods (crops, vegetables, fruits, meats, eggs, dairy products)**
   Exposures are estimated referring to the data collected, study reports etc. carried out by the Ministry of Health, Labour and Welfare.
5) **Exposure via household products**
   Exposures from each product are estimated with its usage taken into account.

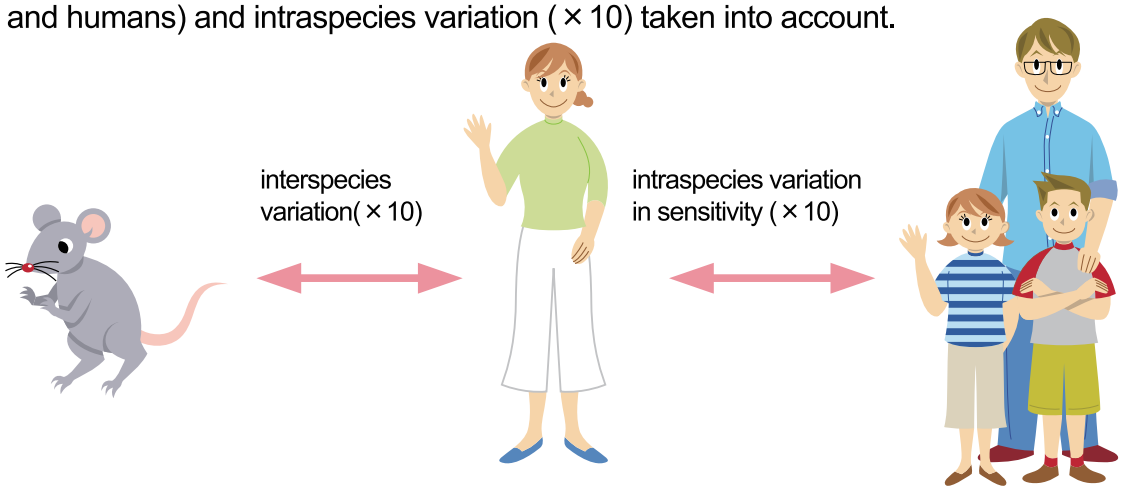
   Absorption rate is deemed to be 100% unless specific data on human metabolism etc. are available.

UF (Uncertainty Factor)

Various data used for risk assessment involve many uncertain elements.

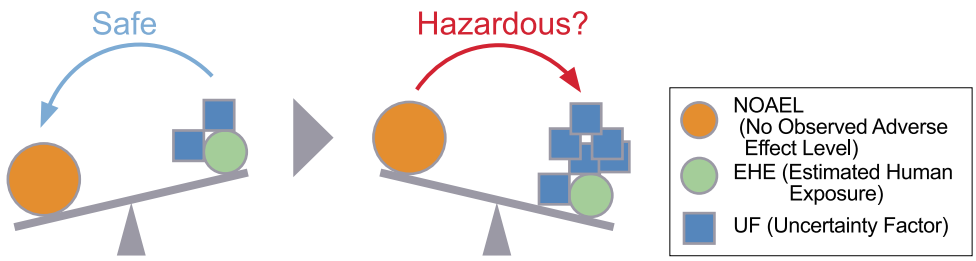
(For example, it is impossible to prove that the carcinogenicity of a chemical in humans appears at a probability of 1 in a million, by conducting a test involving the exposure of 1 million human subjects to the chemical for the rest of their lives. For this reason, experiments using rats and other experimental animals are carried out instead of humans. The carcinogenicity of a chemical in humans, estimated on the basis of the data from these, toxicity tests, involved uncertainties.)
In risk assessment, UF (Uncertainty Factor) is set to enable risk assessment while avoiding underestimation of the risk due to uncertainties so that risk assessment can be done with a sufficient safety margin.

Generally, UF is initially set at 100, with interspecies variation (× 10, difference between animal and humans) and intraspecies variation (× 10) taken into account.



UF is supplemented if there is any uncertainty related to the study period, reliability and other features of the toxicity tests. UF is basically 1 or 10 but can assume other values depending on the degree of uncertainty. (At present, there are no global rules about UF. Individual countries and evaluation organizations select a value of UF deemed as appropriate.)
When multiple factors are taken into consideration, the factors are multiplied by each other to yield UFs (product of Uncertainty Factors).

As this value gets higher, the Risk Assessment becomes less reliable.
If this value is excessively high, it is possible that “no risk” is judged to be “a risk” because of low reliability of the data used as the rationale.
So, it is essential to carefully interpret the results of risk assessment.



Terms such as coefficient of explanation, evaluation coefficient, correction coefficient and safety coefficient are sometimes used with the same meaning as UF (Uncertainty Factor).

*"Initial Risk Assessment Report" under the NEDO Project shows UFs (product of Uncertainty Factors) on the following website.
http://www.safe.nite.go.jp/english/risk/initial_risk.html

UFs (product of Uncertainty Factors) = (interspecies variation) × (intraspecies variation) × (use of LOAEL (Lowest Observed Adverse Effect Level) × (test period) × (correction coefficient)

UF for each factor is shown below.

Interspecies variation : 10 (based on toxicity test data),
1 (based on human data)

Intraspecies variation : 10

The use of LOAEL (Lowest Observed Adverse Effect Level)
: 10 (if LOAEL is converted into NOAEL),
1 (if NOAEL is used)

Test period (if short-term test data is used)
: 10 (1-month test),
5 (3-month test),
2 (6-month test),
1 (6-month or longer test)

Correction coefficient:
: A coefficient added at the expert's judgment, depending on the type, quality, etc. of the test. If there is no addition, correction coefficient is set at 1. This coefficient involves the following viewpoints, for example:
- Reliability (whether or not the GLP* requirements are satisfied)
- Differences in routes of exposures (e.g., conversion of respiration-mediated risk into food-mediated risk)

Footnote

*GLP (Good Laboratory Practice): GLP system is aimed at ensuring reliability of test results through checking the operational management, testing facilities, test plans, internal audit system, reliability guarantee system, test results and so on. Every three years, confirmation and renewal is necessary.

Details are given on the page on the GLP System of the NITE website.
http://www.safe.nite.go.jp/english/kasinn/glp.html

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