CHAPTER 2

Risk Concepts

By the end of this section you should:

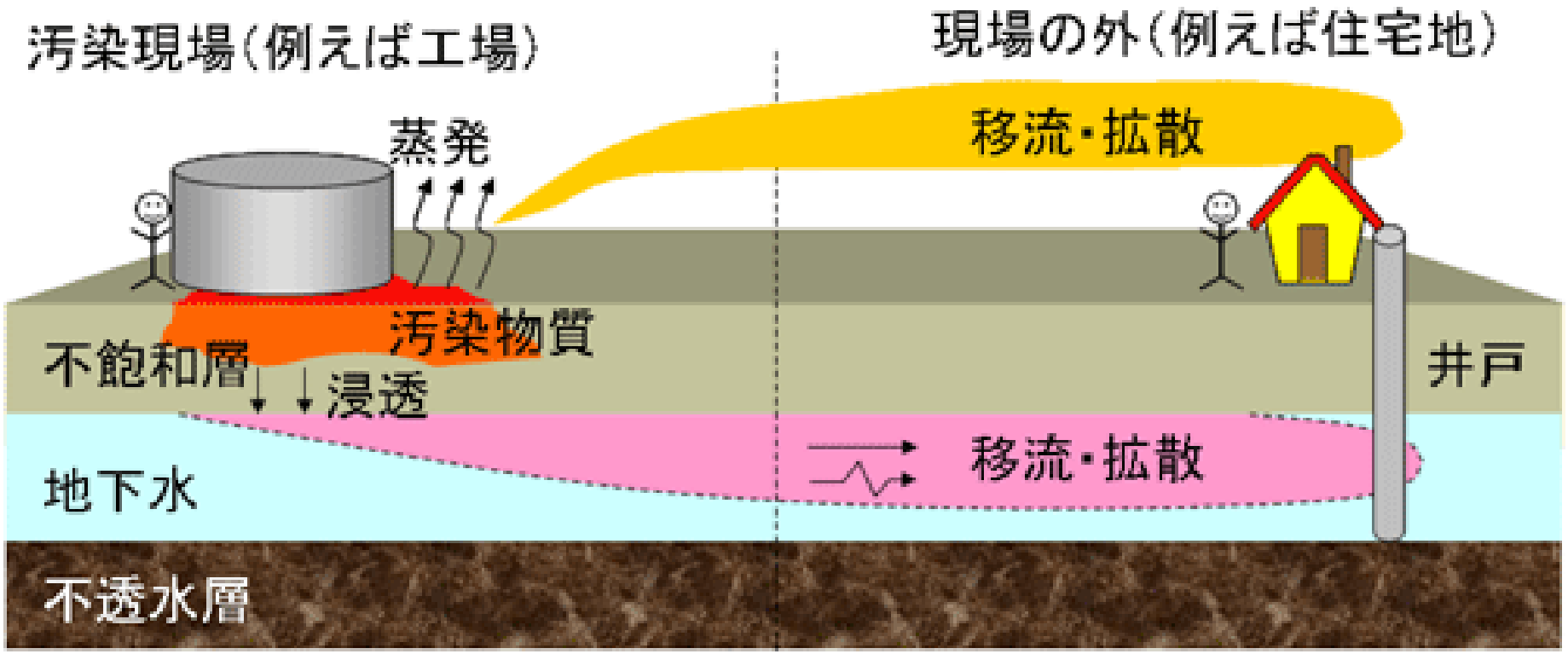
- Be aware of the description of risk

- Be aware of risk assessment concepts

- Understand conceptually

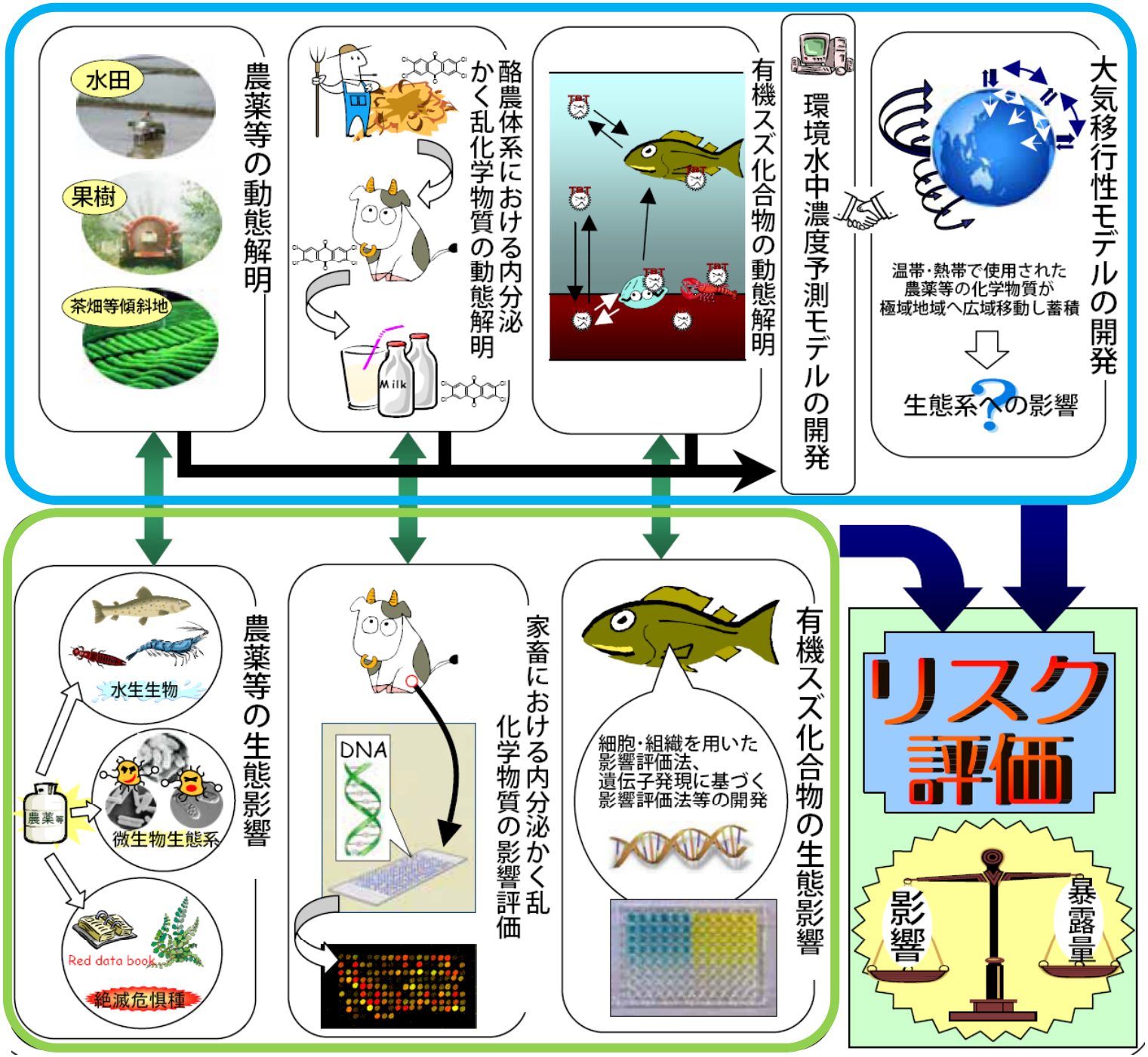
how risk assessment is performed

地圏環境リスク評価システムを開発



農業生態系における化学物質のリスク評価

背景


農薬等の動態解明
水田
果樹
茶畑等傾斜地
酪農体系における内分泌かく乱化学物質の動態解明
Milk
有機スズ化合物の動態解明
環境水中濃度予測モデルの開発
大気移行性モデルの開発
温帯・熱帯で使用された
農薬等の化学物質が
極域地域へ広域移動し蓄積
生態系への影響
農薬等の生態影響
水生生物
農薬等
微生物生態系
Red data book
絶滅危惧種
家畜における内分泌かく乱化学物質の影響評価
DNA
有機スズ化合物の生態影響
細胞・組織を用いた
影響評価法、
遺伝子発現に基づく
影響評価法等の開発
リスク評価
影響
暴露量

Risk:

the probability that a substance or situation will produce harm under specific conditions.

Risk is a combination of two factors:
the probability that
an adverse event will occur
and
the consequences of the adverse effect

Risk assessment:

A systematic, analytical method used to determine the probability of adverse effects.

A common application of risk assessment methods is to evaluate human health and ecological impacts of chemical releases to the environment.

Contents

2.1 Introduction

Term Risk: multifaceted

- Finance (*rate of return for a new plant or capital project, process improvement, etc.)*
- Raw materials supply *(single supply)*
- Plant design and process change

  (new design, impact on bottom line)
- Site selection *(foreign, political stability)* ⇨ 개성

Risk Assessment

- Environmental risk and risk assessment as applied to chemical manufacturing, processing or use
- Impact of exposure to chemicals on human health or environment

2.2 Description of Risk

Risk can be grouped into three general categories

- **Bungee jump → Voluntary risk**
- **Tsunami(쓰나미) → Natural disasters**
- **Food poisoning → Involuntary risk**

1. Voluntary Risk: Things done for a living or for fun (firefighting, sky diving, bungee cord jumping, etc). The risk (danger) is usually obvious and the activity is usually done by **free will** (i.e., a known risk) *determined by actuarial-base statistics (fatalities are correlated by activity, location, other parameters)*

보험통계회계 기초

2. Natural Disasters: Floods, hurricanes, earthquakes, meteorite hits, and other disasters are **beyond human control**; exposure to the effects of certain natural disasters can be exacerbated by actions such as living on a known earthquake fault or the hill side of a volcano (i.e., a known risk). *determined by actuarial-base statistics*

보험통계회계 기초

3. Involuntary risk: An individual or entity releases a compound into the environment (pesticides, known carcinogens or pathogens in food, occupational exposure to chemicals), creating a nuisance that could potentially harm industrial workers or members of the public, who cannot control the exposure. *determined by inferred data (animal tests, analogs, extrapolation)*

추론값 기초

Table 2.1-1 Loss of life expectancy from various societal activities and phenomena

Risk Factor	Loss of life expectancy (days)
Cancer risks associated with environmental pollutants	
Indoor Radon	30
Worker chemical exposure	30
Pesticide residues in food	12
Indoor air pollution	10
Consumer products use	10
Stratospheric ozone depletion	22
Inactive hazardous waste sites	2.5
Carcinogens in air pollution	4
Drinking water contaminants	1.3

Table 2.1-1 Loss of life expectancy from various societal activities and phenomena

Risk Factor	Loss of life expectancy (days)
Noncancer risks associated with environmental pollutants	
Lead	20
Carbon monoxide	20
Sulfur dioxide	20
Radon	0.2
Air pollutants (e.g., carbon tetrachloride, chlorine, etc.)	0.2
Drinking water contaminants (e.g., lead, pathogens, nitrates, chlorine disinfectants, etc.)	0.2
Industrial discharge into surface water	Few minutes
Sewage treatment plant sludge	Few minutes
Mining wastes	Few minutes

Table 2.1-1 Loss of life expectancy from various societal activities and phenomena

Risk Factor	Loss of life expectancy (days)
Lifestyle/demographic status risks	
Being an unmarried male	3500
Smoking cigarettes and being male	2250
Being an unmarried female	1600
Being 30% overweight	1300
Being 20% overweight	900
Having less than an 8th-grade education	850
Smoking cigarettes and being female	800
Being poor	700
Smoking cigars	330
Having a dangerous job	300
Driving a motor vehicle	207
Drinking Alcohol	130
Having accidents in the home	95
Suicide	95
Being murdered	90
Misusing legal drugs	90

Demographic: 인구 통계학

Chemical Risk

Chemical risk is normally defined as the probability for an individual to suffer an adverse effect from an event.

What is the probability that certain types of cancer will develop in people exposed to aflatoxin in peanut products or benzene from gasoline?

What is the likelihood that workers exposed to lead will develop nervous system disorders?

Chemical risk from toxic chemicals can be expressed as follows:

Chemical risk = f (Hazard, Exposure)

aflatoxin: [생화학] 아플라톡신 (발암성독소)

Chemical risk = f (Hazard, Exposure)

- Hazard: *potential for a substance or situation to cause harm or to create adverse impacts on persons or environment.*

- Exposure: *magnitude and length of time of the organism is in contact with environmental contaminant, including chemical, radiation, or biological contaminants.*

- Risk probability: *fraction without unit*

0.0 : no risk

1.0: outcome will occur

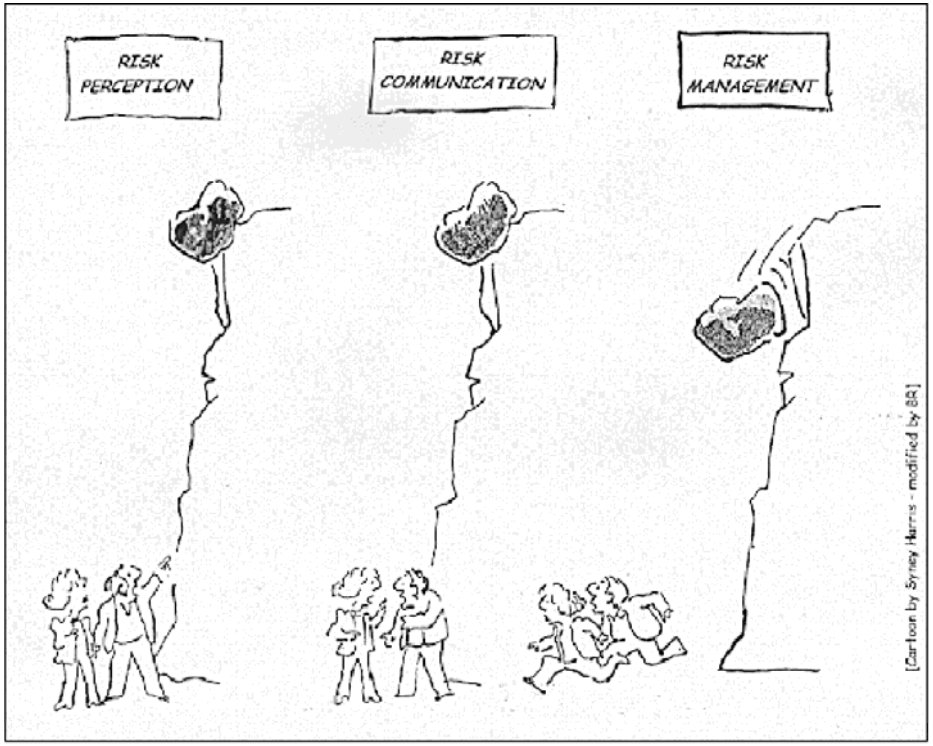
Example:

Three pumps that are all transporting the same chemical (same hazard), but one pump has a seal leak. Which pump poses the greatest risk to the worker? The pump with the seal leak has the greatest potential for exposure, while hazards are equal (same chemical), so the seal leak pump poses the greatest risk.

Three pumps that are all transporting the different chemicals; which one poses the greatest risk to the workers? In this case, we need to examine the hazard of each of the chemicals, as well as the operation of the pumps to determine which poses the greatest risk.

Definitions: Risk vs. Hazard vs. Exposure

Risk = *f* (Hazard, Exposure)



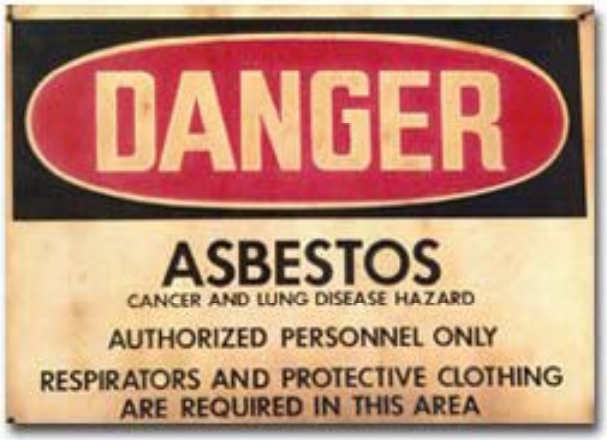
The HAZARD is the loose rock.

The EXPOSURE is standing at the base of the cliff.

In this course, we will rely on information in the literature to identify hazards; we will be primarily concerned with identifying exposures associated with chemical processes. This will involve multiple steps:

Estimate emissions ⇨ (Chapters 8, 11)	**Evaluate fate in ⇨ the environment (Chapter 5)**	**Estimate exposure, dose and response (Chapter 6)**

Synergistic effect asbestos smoking lung cancer



Asbestos Exposure, Lung Cancer and Cigarette Smoking

Selikoff compared smoking and non-smoking asbestos-exposed workers and discovered a "multiple" or "synergistic effect" (Selikoff, 1968). He found that men not exposed to asbestos or cigarette smoking had a negligible risk of less than one, called X.

Smoking non-asbestos-exposed workers had a ten-fold increased risk, of 10X. Asbestos-exposed workers had an eight-fold increased risk, or 8X. But smoking asbestos-exposed workers had roughly an 80-fold greater risk than non-smoking non-asbestos-exposed workers.

In other words, the risk was not just additive, i.e., 10+8=18, but multiplicative, i.e., 10x8=80 The risk held regardless of the specific occupation of the asbestos-exposed individual.

(The Health Consequences of Smoking: Cancer and Chronic Lung Disease in the Workplace, A Report of the Surgeon General, 1985, p. 218).

Example 2.2.1: Interaction of Toxic Agents.

370 asbestos workers

4 years study (Selikoff, 1968)

283 smokers → 24 died of bronchogenic carcinoma (기관지암)
87 non-smokers → 0 died of bronchogenic carcinoma

5 years later (Hammond, 1973)

283 smokers → 41 died of bronchogenic carcinoma
87 non-smokers → 1 died of bronchogenic carcinoma

The asbestos worker who smoke have 8 times the risk of lung cancer compared to all other smokers and 92 times the risk of nonsmokers not exposed to asbestos.

Other chemicals and occupational exposures
which appear to act synergistically
with tobacco smoke
include

Radon daughters
Gold mine exposures
Exposures in the rubber industry

Radon daughter (담배 연기에서 검출되는) 유해 방사성 분자

(Lednar, 1977)

2.3 Value of Risk Assessment
in the engineering profession

Risk Assessment may be conceptualized as simply a means of organizing and analyzing all available scientific information that addresses the question, what are the risks associated with a chemical manufacturing process or use of a chemical product?

If an engineer is asked to conduct a comprehensive assessment, such as developing an Environmental Impact Statement for a proposed new facility, a major study of this magnitude would necessitate the formation of a team of appropriate professionals *(engineer, toxicologist, ecologist, chemist, hygienist, medical and legal staff, etc.)*

2.3 Value of Risk Assessment
in the engineering profession

From an engineering perspective, it may be useful to think of risk as safety issues extrapolated from the present to the long term. That is,

safety may be thought of as the likelihood of immediate adverse consequences,

risk as the likelihood of long-term adverse consequences.

Long term risk vs. conventional safety

Chronic exposures from chemicals vs. Chemical accidents

In chemical explosion, it is easy to know the source of the injury or damage. In contrast, it is often extremely difficult to link a local epidemic of cancers to a chemical exposure that may have occurred decades before. The uncertainties associated with long-term risks render them difficult for managers to grapple with effectively.

Epidemic: 전염병의

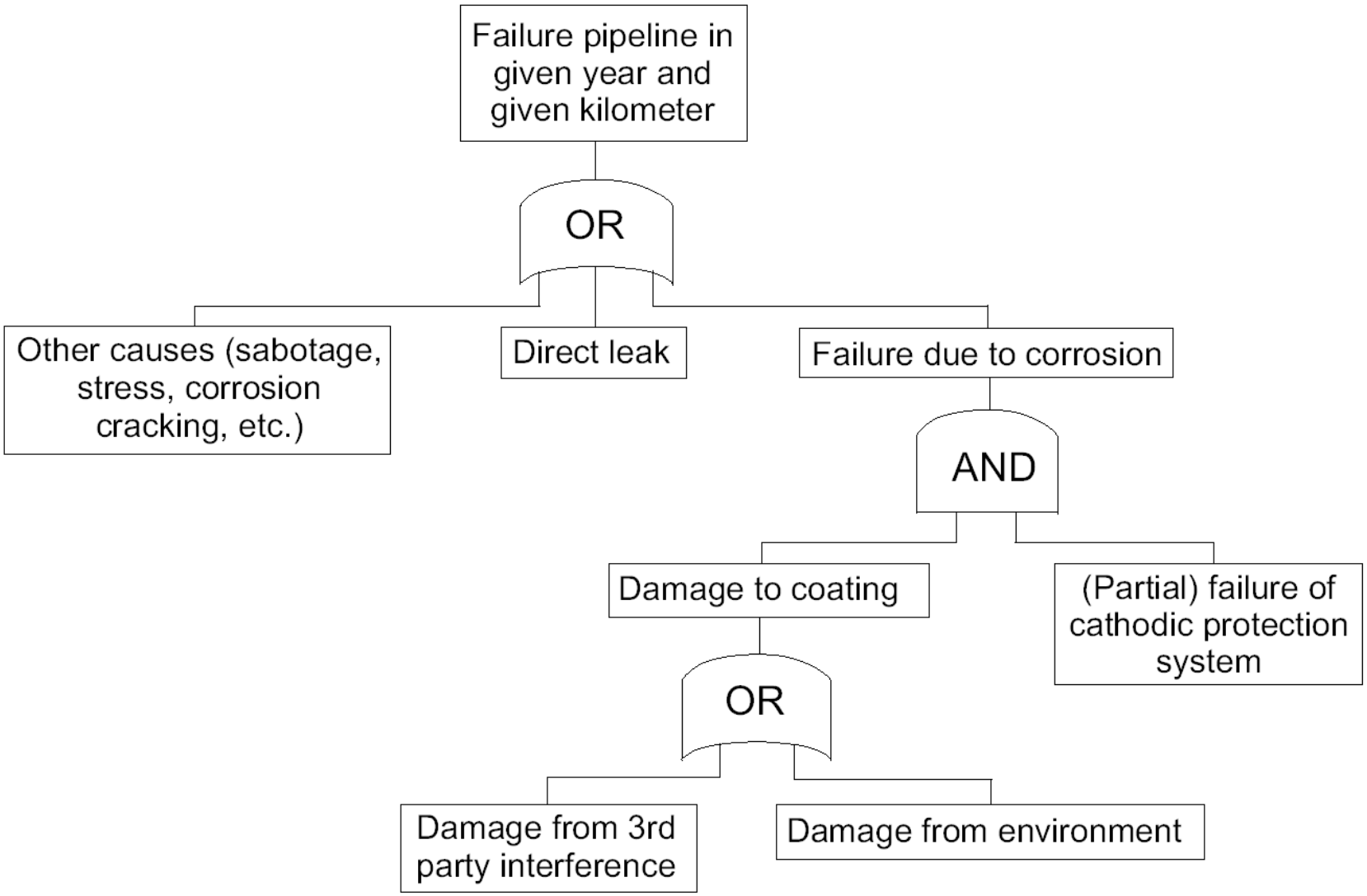
Hazards and Operability Studies (HAZOP)

For chemical accidents, injuries and property damage can be anticipated via some level of **P**rocess **H**azard **A**nalysis (PHA) such as fault tree analysis, or **Haz**ards and **O**perability Studies (HAZOP).

Example 2.3-1: Fault Tree Analysis

Understanding gas pipelines can fail when an operator of construction equipment punctures the pipeline. The pipeline can also fail due to corrosion when the coating separating the pipeline from the soil is damaged and the sacrificial cathode fails to inhibit resulting of the pipe line. Damage to the coating may due to abrasion by human activity or degradation in the environment. Base on this statement, draw a fault tree for the possible failure of a gas pipeline.

Fault tree analysis of gas pipeline demonstrating possible mode of failure



2.4 Risk-Based Environmental Law

Many environmental laws incorporate risk management as a goal of legislation. Some environmental laws consider economic impacts of risk management as well.

Clean Air Act (NAAQS)

protect the public health allowing an adequate margin of safety

These standards mandate protection of public health based only on risk ,without regard to technology or cost factors.

Clean Water Act

requires industries to install specific treatment technologies

"*best practicable control technology" and "best available technology that is economically achievable"*

2.4 Risk-Based Environmental Law

Pesticides are licensed if they don’t cause “any unreasonable risks to man or the environment taking into account the economic, social, and environmental costs and benefits of the use of any pesticide.”.

In other words, economic and other factors may or may not be combined with risk issues as regulations are developed.

Table 2.4-1 lists selected United States safety, health, and environmental statutes that require or suggest human health risk assessment before regulations are promulgated. The list is enormous, and will probably grow with time.

Table 2.4-1 US Safety, health and environmental statues (laws) that imply risk assessment

United States Environmental Protection Agency

Atomic Energy Act (also NRC)	42.U.S.C.2011
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, or Superfund)	42.U.S.C.9601
Clean Air Act	42.U.S.C.7401
Clean Water Act	33.U.S.C.1251
Emergency Planning and Community Right to Know Act	42.U.S.C.11001
Federal Food and Drug, and cosmetics Act (also HHS)	21.U.S.C.301
Federal Insecticide, Fungicide, and Rodenticide Act	7.U.S.C.136
Lead Contamination Control Act of 1988	42.U.S.C.300j-21
Marine Protection, Research, and sanctuaries Act (also DA)	16.U.S.C.1431
Nuclear Waste Policy Act	42.U.S.C.10101
Resource Conservation and Recovery Act	42.U.S.C.6901
Safe Drinking Water Act	42.U.S.C.300f
Toxic Substances Control Act	7.U.S.C.136
Food Quality Protection Act of 1996	7.U.S.C.6

Table 2.4-1 US Safety, health and environmental statues (laws) that imply risk assessment

Consumer Product Safety Commission

Consumer Product Safety Act	15.U.S.C.2051
Federal Hazardous Substance Act	15.U.S.C.1261
Lead-Based Paint Poisoning Act (also HHS and HUD)	42.U.S.C.4801
Lead Contamination Control Act of 1988	42.U.S.C.300j-21
Poison Prevention Packaging Act	15.U.S.C.1471

Department of Agriculture

Eggs Products Inspection Act	21.U.S.C.1031
Federal Meat Inspection Act	21.U.S.C.601
Poultry Products Inspection Act	21.U.S.C.451

Table 2.4-1 US Safety, health and environmental statues (laws) that imply risk assessment

Department of Labor	
Federal Mine Safety and Health Act	30.U.S.C.801
Occupational Safety and Health Act	29.U.S.C.651

Department of Transportation	
Hazardous Liquid Pipeline Safety Act	49.U.S.C.1671
Hazardous Materials Transportation Act	49.U.S.C.1801
Motor Carrier Safety Act	49.U.S.C.2501
National Traffic and Motor Vehicle Safety Act	15.U.S.C.1381
National Gas Pipeline Safety Act	49.U.S.C.2001

2.5 General Overview of Risk Assessment Concepts

A risk assessment should estimate adverse impacts to health or the environment and determine whether these impacts pose a serious threat.

(National Research Council, **NRC**, 1983)

Four Major Components in Risk Assessment

1. **Hazard Assessment.**
2. **Dose-Response.**
3. **Exposure Assessment.**
4. **Risk Characterization.**

Risk Assessment Framework

1. Hazard Assessment:

What are the adverse health effects of the chemical in question?
Under what conditions?
For example, does it cause a certain kind of cancer?

Toxicologists usually perform this analysis. Since this information is pertinent to use a chemical, sometimes hazard information can be obtained from reference data.

Risk Assessment Framework

2. Dose-Response:

How much of the chemical causes a particular adverse effect?
There may be multiple adverse health effects, or responses, for the same chemical at different concentrations. Each adverse effect has a unique dose-response curve. The dose-response curve is non-linear because some member of the population are more sensitive than others.

Dose is defined as the quantity of a chemical that crosses a boundary to get into a human body or organ system. The term applies regardless of whether the substance is inhaled, ingested, or absorbed through the skin. **Dose-response**, then, is a mathematical relationship between the *magnitude of dose* and extent of a certain *negative response* in the exposed population.

Risk Assessment Framework

3. Exposure Assessment:

Who is exposed to this chemical?
How much of the chemical reaches the boundary of a person, and how much enters the person's body?

Exposure may be measured, estimated from models, or even back-calculated from measurements called biomarkers taken from exposed people.

Risk Assessment Framework

4. Risk Characterization:

How great is the potential for adverse impact from this chemical?

What are the uncertainties in the analyses?

How conclusive are the results of these analyses?

Risk Assessment

This general risk assessment framework has been tailored to human health risk assessment from exposure to chemicals. A risk assessment team may decide that specific of the eco-assessment require attention. This level of activity is critical for new plant siting, which must include a thorough examination of the eco systems in-place as well as unique areas (wetland..).

Risk Assessment Process

The risk assessment process can be iterative. That is, if a cursory or screening risk assessment identifies concerns, a more rigorous process may be called for. There are important data gap that need to be filled to render the process sufficiently conclusive for risk management. The data gap may be filled with recommendation for *specific studies* with varying cost and time requirements, such as:

- proceeding with testing for health effects;
- evaluating effectiveness of engineering controls and personnel protective equipment (PPE) to limit exposure;
- defining kinetics and decomposing products of a waste stream and the impact of the chemical waste and its degradation products on local flora and fauna (식물군과 동물군)

Cursory: 서두르는(hurried);마구잡이의, 소홀한(careless); 피상적인

Risk Management

If it is reasonably clear from the risk assessment that a risk exists, the next step is ***risk management.***

- Risk management is the process of identifying, evaluating, selecting, and implementing actions to reduce risk to health and to ecosystems.

- Its goal of risk management is scientifically sound, cost effective, integrated actions that reduce or prevent risks while taking into account social, cultural, ethical, political, and legal considerations.

Risk Management

Risk managers must clearly answers many questions such as,

- What level of exposure to a chemical risk agent is an unacceptable risk?
- How great are the uncertainties and are there any mitigating circumstances?
- Are there any trade-offs between risk reduction, benefits, and additional costs?
- What are the chances of risk shifting, that is, transferring risk to other populations?
- Are some of the risks worse than others ?

The answers to these questions often depend on the culture and values of the organization that commissioned the risk assessment.

2.6 Hazard Assessment

A hazard is an adverse effect related to chemical exposure

A chemical exposure hazard assessment answers the question:

What are the adverse effects of chemical?

Cancer (癌)？

Endocrine disruption (内分泌系 攪亂物質)？

Example 2.6-1: Endocrine Disruptors

There is evidence that domestic animals and wildlife have suffered adverse consequences from exposure to environmental chemicals that interact with the endocrine system.

Endocrine Disruptors :

Organochlorine pesticides,
PCBs,
Dioxins,
Synthetic and plant derived estrogens

→

Decline in the quantity and quality of sperm production in humans over last four decades.

2.6.1 Cancer and Other Toxic Effects

Cancer can be caused by two different types of chemical substances: Genotoxic carcinogens and nongenotoxic carcinogens

● Genotoxic chemicals:

- *No threshold amount below which they will NOT cause cancer*
- *Theoretically, one molecule of a genotoxic carcinogen could alter DNA and cause a mutation.*
- *Such an exposure at this level would not cause cancer due to natural repair mechanism for internal damage.*
- *Genotoxicity is generally assumed (lack of mechanistic study).*

● Nongenotoxic chemicals:

- *have a safe threshold quantity*
- *nongenotoxic substances are analyzed much like chemical endpoint.*

Mutation:돌연변이

2.6.2 Hazard Assessment for Cancer

US EPA has developed guidelines
for hazard assessment of chemical carcinogens.

Group A:	Carcinogenic to humans (There are currently only about 20 of these chemicals)
Group B1:	Probably carcinogenic to humans based on limited human evidence of carcinogenicity
Group B2:	Probably carcinogenic to humans based on sufficient animal evidence, but inadequate human evidence
Group C:	Possibly carcinogenic to humans
Group D:	Not classifiable for human carcinogenicity
Group E:	Evidence of non-carcinogenicity for humans

Hazard Assessment for Cancer

Organizations other than US EPA have developed alternative guidelines for toxic chemicals.

For example, Table 2.6-1 lists thirteen chemical substance regulated by OSHA as human carcinogens.

Due to the ecotoxic concerns of these chemicals, many are no longer in commerce and/or have been replaced with less hazardous alternative chemistries.

Table 2.6-1 *Thirteen OSHA –regulated carcinogens (29CFR 1910.1003)*

Table 2.6-1 Thirteen OSHA-Regulated Carcinogens (29CFR 1910.1003).

CAS Number	Chemical Name	Previous Use
53-96-3	2-Acetylaminofluorene	hazardous air pollutant—no use
92-67-1	4-Aminodiphenyl	antifungal agent
92-87-5	Benzidine	manufacture of azo dyes
542-88-1	Bis-chloromethyl Ether	manufacturing ion exchange resins
91-94-1	3,3'-Dichlorobenzidine	manufacture of azo dyes, yellow pigments
60-11-7	4-Dimethylaminoazo-benzene	pH indicator
151-56-4	Ethyleneimine	treatment (etherification) of cotton
107-30-2	Methyl Chloromethyl Ether	manufacturing ion exchange resins
134-32-7	Alpha-Naphthylamine	manufacturing dyes
91-59-8	Beta-Naphthylamine	manufacturing dyes
92-93-3	4-Nitrobiphenyl	manufacturing p-biphenylamine
62-75-9	N-Nitrosodimethylamine	antioxidant in lubricants, polymer softener
57-57-8	Beta-Propiolactone	disinfectant

OSHA: Occupational Safety and Health Administration
CAS: Chemical Abstracts Service

Example 2.6-2 Cancer Slope Factor

To calculate the slope factor for acrylonitrile
Producing brain tumors in Fischer 344 female rats by administering the carcinogen in drinking water for 24 months.

Dose (mg/kg-day)	Brain tumor incidence	Brain tumor Incidence	Excess Risk	Linear Estimate of Excess Risk
0	1/179	0.0056		
0.12	1/90	0.0111	0.0055	0.0028
0.36	2/91	0.0220	0.0164	0.0084
1.25	4/85	0.0471	0.0415	0.0292
3.65	6/90	0.0667	0.0611	0.0853
10.89	23/88	0.2614	0.2558	
Σ16.27			Σ0.3802	

Fit the data with a linear equation, excess deaths = m* dose rate (mg/kg-day), where m is the slope factor. Finally compare the deaths predicted with the regression data with the observed frequencies.

$$m = \frac{\sum(excess\ risk)}{\sum(dose, mg/kg \cdot day)} = \frac{0.3802}{16.27} = 0.0234 \frac{mg}{kg \cdot day}$$

Example 2.6-2 Cancer Slope Factor

Fit the data with a linear equation,

Excess deaths = m x Dose rate (mg/kg-day)

where m is the slope factor.
Finally compare the deaths predicted with the regression data with the observed frequencies.

$$m = \frac{\sum(excess\ risk)}{\sum(dose, mg/kg \cdot day)} = \frac{0.3802}{16.27} = 0.0234 \frac{kg \cdot day}{mg}$$

2.6.3 Hazard Assessment for Non-Cancer Endpoints

Adverse effects other than cancer and gene mutation are generally assumed to have a dose or exposure threshold. As a result, a different approach is used to evaluate potential risk for these non-cancer effects, which include liver toxicity, neurotoxicity, and kidney toxicity.

Approach

Identification of a critical effect for which the magnitude of the response can be assessed:

RfD (Reference Dose) = "an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime". (US EPA 2000) mg pollutant/kg body weight/day

RfC (Reference Concentration) = "expressed as a concentration or mg/m^3 . It is the baseline "safe" dose or concentration to which a real exposure may be compared (US EPA 2000)

US EPA, Terminology Reference System (TRS 2.0) *http://oaspub.epa.gov/trs/prc_qry.keyword.htm*

Derivation of RfD or RfC

The RfD or RfC is usually based on the most sensitive known effect- i.e. the effect that occurs at the lowest dose.

Deriving RfD / RfC involves determining NOAEL or LOAEL from an appropriate animal study or human epidemiology study, and applying various uncertainty and modifying factor to arrive at the RfD/RfC. The combination of these uncertainty factors can result in highly conservative interpretations

- **NOAEL** (no-observed-adverse-effect level) [mg/kg-day]
- **LOAEL** (lowest-observed-adverse-effect level) [mg/kg-day]

Epidemiology: 역학, 의 생태학, 유행병학

Example 2.6-3: Reference Dose

Reference doses are used to evaluate noncarcinogenic effects resulting from exposure to chemical substances. RfD is the threshold of exposure below which protective mechanisms are believed to guard an organism from adverse effects resulting from exposure over a substantial period of time.

When valid human toxicological data are available, it forms the basis for the reference dose. When human exposure data are not available, the animal species believed to be most sensitive to the chemical of concern is used to determine the lowest level at which an adverse effect is detected, often called the LOAEL. Similarly the NOAEL is the greatest test-dose level at which no adverse effect is noted.

When animal data are used, the reference dose for human populations is adjusted by extrapolation factors to convert the NOAEL or LOAEL into reference dose.

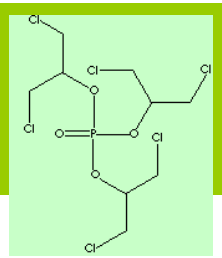
Example 2.6-3: Reference Dose

$$RfD = \frac{NOAEL}{F_A F_H F_S F_L F_D}$$

F_A : Adjustment factor to extrapolate from animal to human populations
F_H : Adjustment factor for differences in human susceptibility
F_S : Adjustment factor used when data are obtained from subchronic studies
F_L : Adjustment factor applied when the LOAEL is used instead of the NOAEL
F_D : Adjustment factor applied when the data set is dubious or incomplete

Each adjustment factor should account for the systematic difference between the two measures bridged by the extrapolation and incorporate a margin of safety in accordance with the uncertainty associated with the extrapolation.

Example 2.6-3: Reference Dose



In a 3-month subchronic study in mice, the NOAEL for tri (1,3-dichloro-2-propyl) phosphate was 15.3 mg/kg body weight per day; LOAEL was 62 mg/kg at which dose abnormal liver effects were noted. If each of the adjustment factors is equal 10, the reference dose for this chemical is:

Using the NOAEL:

$$RfD = \frac{NOAEL}{F_A F_H F_S} = \frac{15.3\ mg/kg \cdot day}{10 \times 10 \times 10} = 0.015\ mg/kg \cdot day$$

Using the LOAEL:

$$RfD = \frac{LOAEL}{F_A F_H F_L F_S} = \frac{62\ mg/kg \cdot day}{10 \times 10 \times 10 \times 10} = 0.0062\ mg/kg \cdot day$$

0.0062 mg/kg-day would be selected as the RfD for human.

Structural Activity Relationships (SAR)

effective method for estimating hazard and other properties (Chap 5)

- SAR: structural property of a molecule and its biological activity

Approach

- Choosing appropriate structural analog

  (structure, substructure, physicochemical properties, etc.)

  Ex) acrylamides, vinyl sulfones, dianilines, sulfoniums, epoxides, benzo-thiazoliums, hindered amines, acrylates, and dichlorobenzene pigmentetc.
- Health effects: *absorption into body, metabolism, capability of tumors(oncogenicity), DNA mutations, acute, chronic, neurotoxicity, reproductive effects, stc.*
- Information of environmental fate ***(details in Ch. 5)***

☮ ***Intrinsic uncertainty***: extrapolating information from one chemicals to another

Available Hazard References

References used to inform hazard assessment (further are in Appendix F)

1. MSDS. Material Safety Data Sheet

documented by chemical manufacturers. Contains safety, hazard, physicochemical prop, precaution for handling, etc.

2. NIOSH Pocket Guide to Chemical Hazards

NIOSH(National Inst. for Occupational Safety and Health)
PEL (Permmissible Exposure Limit concentration) by OSHA
www.cdc.gov/niosh/npg/pgdstart.html

3. IRIS. Integrated Risk Information System.

Database of *Health effects by US EPA.*
http://www.epa.gov/ngispgm3/iris/index.html

Available Hazard References

4. **HSDB**. Hazardous Substances Data Bank. (HSDB®)

   Toxicology data file by the National Library of Medicine
   http://chem.sis.n;m.nih.gov/hsdb/

5. **Toxnet**. By National Library of Medicine. (IRIS and HSDB)
   http://sis.nlm.nih.gov/sis1/

6. **Books**. ☆ *"Toxicology, the Basic Science of Poisons"*,
   Casarett & Doull, Macmillan, 1995),
   ☆ "Patty's *Industrial Hygiene and Toxicology*",
   Patty, John Wiley & Sons

7. **ACGIH**. American Conf. of Governmental Industrial Hygienists.
   Chemical exposure limit like TLVs (Threshold Limit Values)
   Voluntary action

2.7 Dose-Response

- **Dose-Response is a graph of quantitative relationship between exposure and toxic effect.**

- **This analysis enables risk assessors to estimate a “safe” dose.**

- **To estimate risk, actual dose is compared to safe dose.**

2.7 Dose-Response

Dose-response answers the the question:

- **How large a dose cause what magnitude of effect?**

Larger doses cause greater and more serious effects. For a given chemical, there is a separate curve for each adverse health effect.

2.7 Dose-Response

The basic shape of the dose-response curve is determined by the biological mechanism of action. On a subtler level, the curve illustrates the sensitivity of different members of the population.

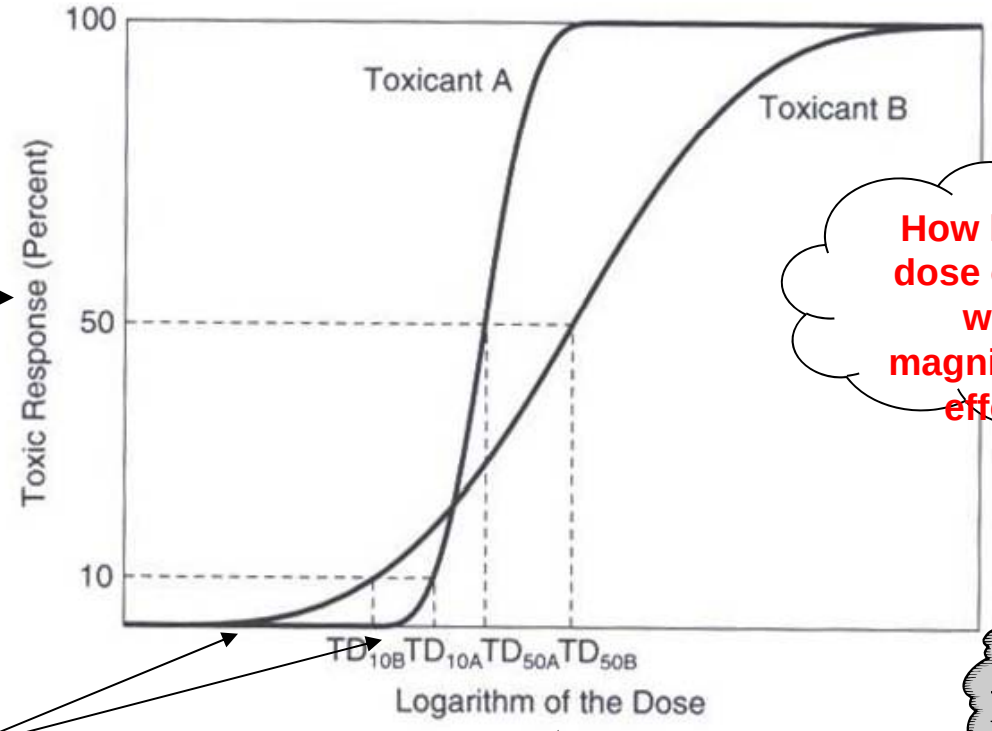
It is a plot of dose in mg chemical per kg of body weight, versus percent of the population affected by that dose.

For example, an LD50, or lethal dose 50%, is a statistic frequently tabulated for some chemicals. It is the dose, in mg/kg, at which 50% of the rats or other tested species die. This statistic emerges from a dose-response assessment.

2.7 Dose-Response

quantitative relationship between exposure and toxic effect

% of the population affected by that dose



How large a dose causes what magnitude of effect?

No toxic effect

Dose (mg chemical / kg of body weight)

LD50 (Lethal dose 50%) : It is the dose (mg/kg) at which 50% of tested species die.
Threshold Exposure Limits (**TLVs**) and Permissible Exposure Limits (**PELs**) to generate dose-response curves.

2.7 Dose-Response

Rat, mice and rabbits are frequently tested species. They are like humans in that they are mammals, but they are also small, and breed and mature quickly, which is make the testing process more manageable.

Nonetheless, these species may react differently from humans to exposure to a particular chemical. Significant research efforts have been under way for some time to find reliable substitutes for animal testing of chemical hazards.

Rodent (설치류)= Rat (쥐), mice(새앙쥐) and rabbits (집토끼)

2.7 Dose-Response

The curvature of the dose-response curve illustrates the varying sensitivity of different members of the exposure population.

That is, if sensitivity to the chemical were constant, dose-response would be a straight line.

The curvature illustrates that some people (or, more likely, rodent) are especially vulnerable, while others are more resistant. Among humans, common examples of sensitive subpopulations are children, the elderly, and the immunosuppressed.

Vulnerable 공격받기 쉬운
immunosuppressed. 면역결핍

Example 2.7-1 Which chemical is more toxic?

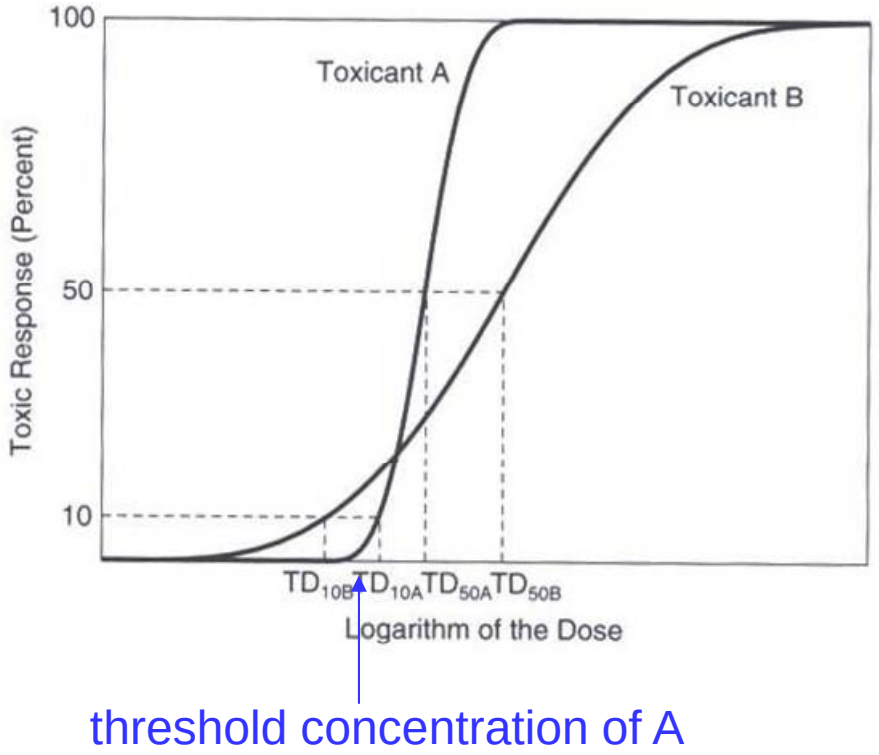


Fig. 2.7-1 Dose-response curves for two compounds that have different relative threshold limit values

The toxic response of two chemicals A and B, as a function of dose.

Chemical A has a higher threshold concentration, at which no toxic efforts are observed, than chemical B.

Once the threshold dose is exceed, chemical A has a greater response to increasing dose than chemical B.

If the TLV were based on the dose at which 10% of the population experienced health effects, then chemical B would have a lower TLV than chemical A.

If the TLV were based on the dose at which 50% of the population experienced health impacts, chemical A would have the lower TLV.

The answer depends on the precise definition of toxicity and the specifics of the dose-response relationship.

2.7 Dose-Response

Developing the data to support a dose-response curve is expensive, time consuming, and rigorous.

It is generally not performing until some screening has suggested that it could be useful. When this testing is performed, it often begins with a rangefinder study. The purpose of this preliminary study is to determine what order of magnitude of dose generates adverse effects. This improves the quality of the dose-response testing.

2.7 Dose-Response

The outcome of the overall dose-response effort helps tell the assessor what the toxicological endpoint of concern is.

Are we concerned about neurotoxicity in young children, whose nervous system is still developing? Are we studying cancer in a particular organ?

The dose-response study also provides the NOAEL (no-observed-adverse-effect-level) and the benchmark dose (**BMD**). These quantities can provide a basis for risk assessment.

2.7 Dose-Response

Since dose-response testing is so resource-intensive, risk assessors sometimes use structural-activity relationships to estimate a NOAEL or BMD, generally incorporating a coefficient to account for uncertainty. That is, we find a chemical whose NOAEL or BMD is known and has similar (chemical) functional groups to the substance of interest. The structural analog is then used to estimate a NOAEL or BMD for the substance with no dose-response curve available.

For cancer, dose-response analysis is appropriate for Group A and B substances. Fewer than 10% of the 80,000 or so chemicals in commerce currently have dose-response curves.

2.7 Dose-Response Analysis

There are several important concern associated with dose-response analysis

1. Different species may have different responses. We don't know if humans are more or less sensitive than the most sensitive species of rodent. In the absence of data, risk assessors use a safety factor of 10 to account for this uncertainty. With data, a scaling factor of body weight to the ¾ power is used to convert from rodents to human. Similar scaling factor are available for a large number of laboratory animals.

2.7 Dose-Response Analysis

2. Very high doses, to the point of acute poisoning of the test animal are sometimes necessary to generate a statistically significant effect. The shape of the curve below the lowest dose tested is truly unknown, and often very relevant. Actual exposure are well below the lowest tested dose. Models have been developed to approximate this portion of the dose-response curve.

2.7 Dose-Response Analysis

3. Since it may take a long time for cancers to be detected in laboratory animal tests, some otherwise well-designed experiments may have been too brief. Further more, the time-to-tumor may be a function of dose, which further complicate the entire analysis.

4. The route of exposure can also effect the outcomes of an analysis. For example, Chromium (VI) is hazardous when inhaled; however, laboratory experiments may have not shown evidence that exposure through ingestion causes any adverse effects. Therefore, it is extremely important to be cognizant of the route of exposure when assessing risk.

인식하고 있는

2.8 Exposure Assessment

Exposure: The amount of a substance that comes into contact with the external boundaries of a person

Dose: The quantity that crosses the external boundary

Internal dose: The amount of absorbed

Bioavailability: The ratio of the internal dose to exposure

2.8 Exposure Assessment

Exposure Pathways

(1) Dermal: hand contact, bioavailability to body is low, ~5 %

(2) Inhalation: by the form of vapor, aerosol, or solid particulates, often very harmful, bioavailability to body is ~100 %

(3) Ingestion: eating and drinking in workplace, danger

(4) Percutaneous: Injection

Percutaneous: 주사 따위에 찔러서

2.8 Exposure Assessment

Assessing Exposure

The preferred approach for assessing exposure is to use personal monitoring data for the chemical of interest at the site. If not available, monitoring data for the chemical at sites with similar operations is the next choice.

If there are no data available on the chemical of interest, exposure can be assessed using data for the surrogate chemical. A surrogate chemical is one whose physical and chemical properties are as similar as possible, and is used in similar operations.

Finally, in the absence of any relevant data, exposure can be assessed using models. For example, a mass balance model can be used to estimate inhalation exposure to vapors.

2.8 Exposure Assessment

http://www.epa.gov/ceampubl/

U.S. Environmental Protection Agency

Exposure Assessment Models

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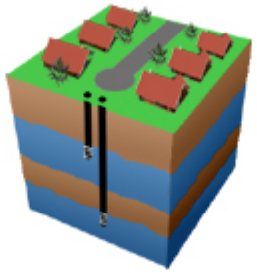
The **EPA Center for Exposure Assessment Modeling (CEAM)** was established in 1987 to meet the scientific and technical exposure assessment needs of the United States Environmental Protection Agency (U.S. EPA) as well as state environmental and resource management agencies. CEAM provides proven predictive exposure assessment techniques for aquatic, terrestrial, and multimedia pathways for organic chemicals and metals.

Groundwater Models

Groundwater models quantify the movement of subsurface water and provide inputs to subsurface contaminant transport models. Simulation provides insight into groundwater and contaminant behavior and quantitative assessments for environmental decision making.



Surface Water Models

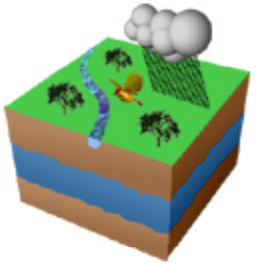
By modeling contaminant movement and concentration in lakes, streams, estuaries, and marine environments, researchers can better understand how exposure to contaminants affects aquatic environments.

Food Chain Models

Contaminated aquatic and terrestrial environments typically result in the bioaccumulation of chemicals within all trophic levels of an ecosystem. Software models provide tools for tracking the movement of contaminants through food chains and for estimating chemical impacts on exposed biota.

Multimedia Models

Contaminants may travel through the atmosphere, soil, surface water, and the organisms that inhabit these media. The multimedia approach to exposure modeling quantifies the impacts of contaminants as they travel through more than one of these environments.



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2.8 Exposure Assessment

Assessing Exposure

A different approach to addressing exposure is to measure some appropriate biomarker. This applies to people who already been exposed. A biomarker is a measurable substance whose presence in the body is a direct result of exposure to the specific chemical. Exposure may be estimated from models and based upon the biomarker measurements.

Unfortunately, there are few substances that pose an exposure concern for which a biomarker has already been identified and measure. Some substances have metabolite which can be detected in blood or urine; these are common testing approaches for biomarkers.

2.9 Risk Characterization

Risk characterization is the amalgamation of available hazard and exposure information - i.e., risk, as well as all major issues developed during the assessments, including the uncertainty of all aspects of the analysis.

It embodies the effects of potential concern, the route and magnitude of the exposed.

Generally, the potential carcinogenicity is assessed using pharmaco-kinetics, chronic toxicity data from analogs and mechanism information (when these data are available)

2.9.1 Risk Characterization of Cancer Endpoints

The classical treatment of cancer risk defines risk as the probability of developing cancer from a particular chemical if a sub-population is exposed to that chemical over a lifetime.

A person can contract cancer from many sources besides exposure to a particular chemical. This concept is called the background cancer level, and must be separated from the probability of developing cancer from a particular chemical exposure.

Thus, risk is defined as the cancer probability in excess of the background cancer level.
(cancer risk = cancer probability – background cancer level)

2.9.1 Risk Characterization of Cancer Endpoints

Our basic equation of risk is

$$\text{Risk} = f(\text{Hazard, Exposure})$$

The basis for cancer risk assessment is the dose-response curve (risk of incidence of cancer vs. dose of an agent).

Since it is assumed that carcinogens do not have thresholds, the “cancer” model generates a non-linear curve. There is never enough data provide a complete dose-response curve. To deal with this reality, the risk assessor is left with the option of applying one of a number of mathematical models to the limited data set so as to describe the relationship.

2.9.1 Risk Characterization of Cancer Endpoints

For a new chemical, with limited dose-response data,

One methodology is to use the slope of the dose-response curve (percent response per mg pollutant per kg of body weight per day) as measure of hazard.

Exposure is the quantity that arrives at the surface of a person's body, in mg of pollutant per kg body weight per day.

2.9.1 Risk Characterization of Cancer Endpoints

For a new chemical, with limited dose-response data,

$$\textbf{Risk} = f(\textbf{Hazard}, \textbf{Exposure})$$

the slope of the dose-response curve (percent response per mg pollutant per kg of body weight per day)

Exposure is the quantity that arrives at the surface of a person's body, in mg of pollutant per kg body weight per day.

This simple application of the basic risk equation often provides the risk manager with sufficient information to make risk management decision.

2.9.2 Risk Characterization of Non-Cancer Endpoints

Non-Cancer risk also has a dose-response curve. The model relationship in this case is linear. Therefore, simplifying assumptions allow us to characterize the risk of adverse health effects as a simple ratio or Hazard Quotient.

The Hazard Quotient is the ratio of estimated chronic dose or exposure level to the RfD or RfC.

Hazard Quotient values below unity imply that adverse effects are very unlikely. The more the Hazard Quotient exceeds unity, the greater the level of concern. However, the Hazard Quotient is not a probabilistic statement of risk.

IQ [知能指數, intelligence quotient], EQ [感性指數, emotional quotient]

2.9.2 Risk Characterization of Non-Cancer Endpoints

Non-Cancer risk = f(Hazard Quotient)

$$\text{Hazard Quotient} = \frac{\text{Estimated chronic dose}}{\text{RfD}} \text{ or } \frac{\text{Exposure level}}{\text{RfD}}$$

Hazard Quotient < 1, adverse effects are very unlikely

Hazard Quotient > 1, the greater the level of concern

Hazard Quotient : 위험지수 (HQ)
Intelligence Quotient: 지능지수 (IQ)
Emotional Quotient:감성지수 (EQ)

2.9.3 Adding Risk

The discussion above presume risk occurs from one chemical at one source. In fact, there are multiple chemicals, mutiple pathways, and multiple exposure route.

It is necessary either to estimate what the most important risks are, or to calculate all sources and pathways.

Aggregate and Cumulative Risk are fairly recent terms in the lexicon. Aggregate means adding risks together from multiple exposure routes: dermal, inhalation, and ingestion.

Lexicon: 사전

2.9.3 Adding Risk

The use of term endpoint becomes important in the emerging area of **Cumulative Risk assessment.**

Sometimes, the risks from one chemical may be too low to generate concern. However, several different chemicals may have the same toxicological endpoint. That is, they affect an organ or system adversely in the same way. Exposure from these chemicals need to be combined to determine whether the adverse effect may occur as a result of a combination of chemical exposures.

SUMMARY

Risk is a quantitative assessment of the probability of an adverse outcome. Risk may result from voluntary exposure to hazardous conditions in one’s occupation, involuntary exposure to radiation, chemicals, pathogens, or the reckless behavior of others, or natural disasters.

SUMMARY

There are four components of risk assessment:

(1) hazardous assessment;

(2) dose-response;

(3) exposure assessment; and

(4) risk characterization.

The engineer should work with chemists, toxicologists, and others when a risk assessment is needed. Although there may be uncertainties in performing risk assessments, it can assist in choosing between process options.

SUMMARY

The risk concept presented will be expanded on in later chapters throughout the text, and their direct application in assessing risk in the manufacturing and use of chemical processes and products will be shown.

Homework #2

Problem 2-5 (a), (b), (c) and (d)

Choice of a Safe Solvent for Photo-resist which consists of an acrylate monomer, polymeric binder, and photo-initiator.

Due date: March 31, 2011