Risk assessment

In the last lecture, I explained the reasons why risk based regulations are considered and partially applied in the drinking water quality standard and so on. Risk assessment requires toxicity assessment and exposure assessment. It means if we want to make a regulation on certain compound, we have to investigate the toxicity of the compounds and to investigate the exposure to the compounds. If we want to know the effect of a compound on human health and if we know only the toxicity of the compounds to animals of certain specie, we need an interpretation of data on the animals to those of human health. If we want to know the effect in the very low concentration range and if we know the results of an experiment carried out in the very high concentration range, we also need an interpretation of the data obtained in the high concentration range to that of the low concentration range.

[Toxicity Assesment]
We need the information of either dose-effect relationship or dose-response relationship in the toxicity assessment.

Dose-Effect Relationship: If we are exposed to some chemical substance, we might have some effect such as sleepy, headache, feel tired, and dearth depending on the dose of exposure.

Dose-Response Relationship: If we can quantify the effect in dose-effect analysis, we call it Dose-Response Relationship.

[Exercise -1 Acute Toxicity]
Piegorsch and Bailer (1997) reported the result on the toxicity of fluoranthene on fathead minnows (a kind of fish). In order to investigate the risk assessment of water pollution, 540 fishes of the kind were divided into 9 groups and kept in separate vessels with different fluorathene concentrations. Their survival numbers after certain time were counted. The result can be summarized as Table 1.

Table 1. The numbers of deaths after exposure to fluorathene of different concentrations

Exposure (μg/L)	0.8	1.4	3.3	3.9	7.5	11.2	11.8	14.5	31.0
Death	1	2	0	1	10	47	46	60	60
Alive	59	58	60	59	50	13	14	0	0
Tested	60	60	60	60	60	60	60	60	60

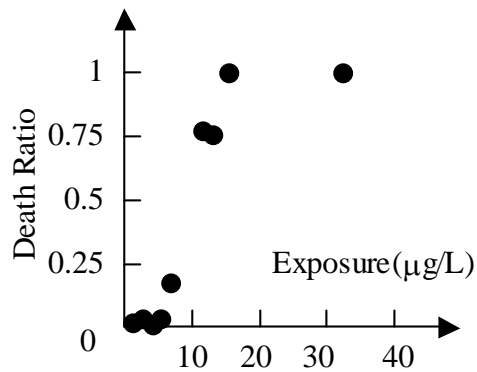Figure 1 shows the dose - response curve which was drawn based on Table 1.

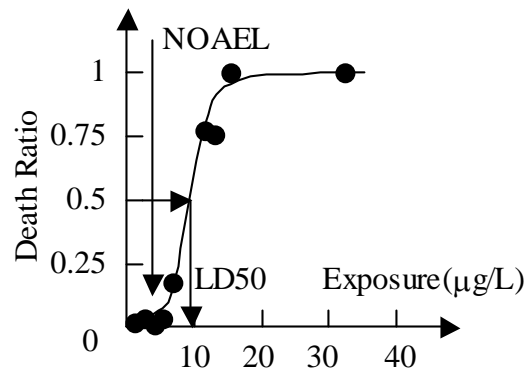Figure 1. Dose Response relationship of fluoranthene on fish of certain specie

Figure 2. Curve-fitting and LD50 determination.

Let us consider obtaining a suitable relation between the expose X and death ratio Y.

1) Why isn't polynomial relation like $Y = a + bX + cX^2 + dX^3$ suitable?

2) Logistic transformation $Z = \log\left(\dfrac{Y}{1-Y}\right)$ is often used to understand this type of data. What is the range of Z corresponding the range of Y [0..1].

3) Obtain the most suitable parameters a and b for the relation $\log\left(\dfrac{Y}{1-Y}\right) = a + bX$.

4) LD50 is a widely used concept which describes the toxicity of chemical compounds. LD50 is defined as shown in figure 2 so that the half of the examined fishes died at that concentration. Please determine LD50 assuming the logistic transformation relation as shown in question 3).

5) NOAEL (No observable adverse effect level) and LOAEL (Lowest observable adverse effect level usually used for the toxicity assessment. Please obtain these concentrations.

In the small dose exposure as is observed in environmental exposure, not only acute toxicity but more chronic effect or carcinogenic effect is important. If we want to test the chronic effect of 10^{-5} lifetime risk level, which is usually the tentative goal of our chemical management, by using rats, we have to keep one million rats for a long time to obtain 10 positively affected rats. Probably, during the long-term experiments, more than 10 rats will die from diseases other than from the chemicals which we want to examine. We can conclude that it is impossible to obtain Dose-Response Relationship in the low concentration exposure of chemicals by experiments. If so, we have to obtain the response by some models based on some assumptions.

[Exercise –2 Cancer Risk]

The following is the result of the exposure experiments of rats to dieldrin, which is a pesticide. The positively affected number of rats were counted after 128 weeks exposure.

Exposure (ppm)	0	1.25	2.50	5.00
Positive rats	17	11	25	44
Negative rats	139	49	33	16
total	156	60	58	60

1) Even in the case of zero exposure, there were several positive rats observed. What will be the background factors causing cancer?

2) In order to eliminate the background factors, please calculate the true positive ratios by using following transformation. Fill in the blanks in the table.

$p*(d) = \gamma + (1-\gamma)p(d)$ where γ is the positive ratio when $d=0$.

d (ppm)	0	1.25	2.50	5.00
$p*(d)$	17/156	11/60	25/58	44/60
$p(d)$	0			

3) Draw a dose-response curve. What is the difference in dose response curve between acute toxicity and carcinogenic toxicity? Can you determine NOAEL ?

4) In the interpretation of the data in dose – response relationship in the carcinogenic effects, following equation is usually used.

$p(d) = F(a + b \log d)$

Three models have been considered.

1- Probit model : $F(x) = \phi^{-1}(x)$ where $\phi(x)$ is the normal distribution function.

2- Logistic model : $F(x) = (1 + e^{-x})^{-1}$

3- Weibull model : $F(x) = 1 - \exp(-\exp(x))$ which means $p(d) = 1 - \exp(-\alpha d^{\beta})$

Please obtain most suitable parameters a and b (or α and β) for the three models respectively.

5) What we want to know is the environmental risk as low as $p=10^{-5}$ which will be caused by low exposure. Although three models give good fitting to the experimental results, three models give quite different doses which cause cancer with the probability of $p=10^{-5}$. Please calculate doses which cause cancer with the probability of $p=10^{-5}$ by using three models. These doses are called VSD (Virtual Safety Dose)s.

In the case of cancer data interpretation, zero exposure is the only solution, if we put the final goal at zero risk. However, if we don't present solutions other than zero, it is very difficult to control the target substance because there is no attainable goal. Sometimes the solution in the zero risk concept will be like that: Use chemical B, whose toxicity is not known instead of chemical A, which is carcinogen. Sometimes the answer is that: Introduce very high cost wastewater treatment to achieve zero risk. High cost wastewater treatments are usually high energy consumption treatments. The treatment of A is very good in terms of pollution control, but it creates other environmental problems like energy consumption, which leads to the global environmental issue.

My understanding is that we should show other solution than zero. In order to estimate the risks in the low concentration level, concept of VSD(Virtual Safety Dose) is introduced for the evaluation of risks from carcinogenic compounds with the no threshold assumption.

I explained that cancer data should be interpreted with no threshold assumption. However, toxicologists consider there should be threshold values below which the effect is negligible even in the case of cancer. Toxicologists present evidences even for the case of cancer caused by X-ray radiation in which the mechanism of cancer seems to have linearity. If we can assume the threshold, we can find experimentally NOAEL(No observable adverse effect level). We can calculate TDI(Tolerable Daily Intake), which is used for regulatory issues by using NOAEL and considering safety factor(Normally 1/100).

[Exercise 3]
In order to convert the data obtained by rats to apply for the calculation of human health risk, the body weight burden is assumed to be equal. It means that the 2mg exposure to 2kg rat equals to 50mg exposure to 50kg man. When we determine the regulations, we consider a safety factor which represent the difference of the species (for example 1/10 for human – rat, 1/2 for human – monkey). Do you feel OK for this procedure? What are the possible differences between rats and human?