Overview of estimation of intake
(Deterministic and probabilistic estimation)

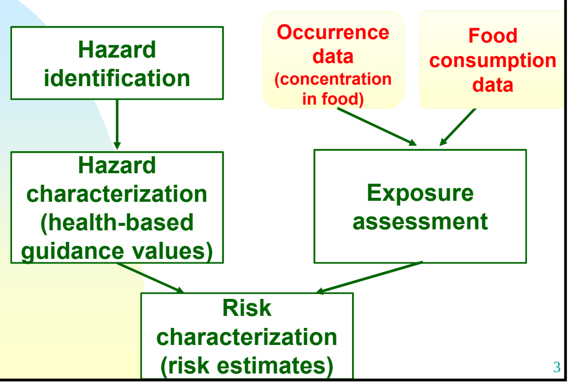
1

Outline

- Estimation of dietary intake
  - Deterministic and probabilistic estimation
  - Long-term (chronic) intake
  - Shor-term (acute) intake
  - Uncertainty analysis
- Comparison of the estimated intake with toxicological reference values
- Recent topics: TTC approach
- Exercise 4: Calculation of dietary exposure by point estimates

2

4 steps of risk assessment in food safety



3

Necessity of estimating dietary intake

- The concept "only the dose makes the poison"
- A magnitude of risk from ingesting a hazard via food may increase or decrease depending on:
  - Concentration of a hazard in food; and
  - Consumption volume of a food containing the hazard
- Health-based guidance values (e.g. PTDI) do not indicate a magnitude of risk
  - Even if the PTDI is extremely low for a hazard, risk from this hazard may be negligible if the hazard is contained only in foods not frequently consumed in significant amount.

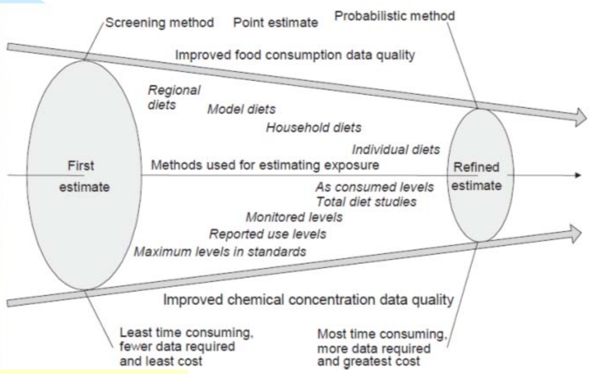
4

Use of information obtained from estimated dietary intake

- Qualitative and/or quantitative information on health risks to consumers can be used for the following:
  - Prioritizing hazards
  - Considering necessity of risk management options
    - Preliminary estimation of risk
    - This usually results in over-estimate
  - Verifying effectiveness of implemented measures
    - Comparison of the dietary intake based on occurrence data before and after implementation of code of practice
  - Checking appropriateness of maximum levels
    - Ensuring the protection of consumers' health

5

Stepwise approach



Source: EHC240 Principles and Methods for the Risk Assessment of Chemicals in Food, Chapter 6, Table 6-1

6

General equation for estimating dietary intake

$$\text{Dietary intake (exposure)} = \frac{\Sigma\,(\text{Concentration of chemical in food} \times \text{Food consumption})}{\text{Body weight (kg)}}$$

- ➢ Estimation of dietary intake should cover
  - ✓ the general population; and
  - ✓ critical groups that are vulnerable or are expected to have significantly different exposures (e.g. infants, children, pregnant women)

7

Data required for estimation of dietary intake

- Essential data
  - ➢ Concentration of a hazard in foods
  - ➢ Food consumption data
    - ✧ information on body weight, age, gender
- Desirable data for refinement
  - ➢ Concentration in edible portion
  - ➢ Effect of processing (e.g. heating, hydrolysis) on concentration
  - ➢ Frequency of food consumption
  - ➢ (At national level,) information on the amount of use and percentage of crops/foods treated for chemicals such as pesticides and food additives

8

Variables in exposure assessment

- Concentration of chemicals in foods
- Amount and frequency of food consumption
  - ➢ may be different among countries/regions

As a result, estimated dietary intake may be different among countries and regions

- Health-based guidance values (e.g. PTDI) or toxicological Point of Departure (e.g. BMDL)
  - ➢ values established by relevant international organizations such as JECFA can be used in the absence of national risk assessment

9

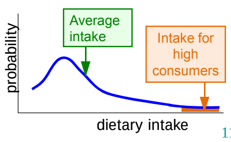
Deterministic (point) estimation of dietary intake

- Provides a single value that describes some parameter of consumer exposure
- Advantages/characteristics:
  - ➢ Easy, not expensive, not time consuming
  - ➢ Many data points are not necessary
  - ➢ Assuming the average or worst-case exposure of a population
- Limitations:
  - ➢ No information on
    - ✧ distribution of consumer exposure
    - ✧ high-end exposure
    - ✧ eaters only vs whole population

10

Probabilistic estimation of dietary intake

- Provides distribution of consumer exposures
- Advantages/characteristics:
  - ➢ Show the information on
    - ✧ high-percentile exposure
    - ✧ eaters only vs whole population
  - ➢ Model the distribution of hazard concentrations
  - ➢ Use food consumption data for each individual
  - ➢ Use Monte Carlo simulation
- Limitations:
  - ➢ Requires extensive data (Occurrence and food consumption)
  - ➢ Requires PC and software



11

Total diet study

- Provides the average long-term dietary intake of chemicals in foods actually ingested by a population
- Fit for screening for purposes to identify the major food groups, contributing to dietary intake of chemicals, for further surveillance
- Advantages/characteristics:
  - ➢ A kind of point estimate
  - ➢ Based on the data on individual foods or food group composites
  - ➢ Can be implemented on a regional basis
  - ➢ Analyze after preparation for consumption → reflect the situation as consumed

12

Two types of total diet study (TDS)

- 'Market basket survey'
  - provides average exposure for a population
  - is used to estimate food groups that may make a significant contribution to dietary intake
  - is not appropriate for
    - a population without consumption data for food groups
    - a chemical present inhomogeneously in a lot
- 'Duplicate portion study'
  - provides exposure from the same diet 'as consumed' by an individual in one day
  - may be used in case of urgency
  - does not identify food groups that may make a significant contribution to dietary intake

13

Market basket survey

- Major steps in "market basket survey" are:
  - To define the population of interest (infants, children, adults, elderly)
  - To identify the core foods using national consumption surveys and estimate their intake by the different populations of interest
  - To sample the selected foods, prepare them "as usually consumed by the population" (i.e. prepared and cooked by the average consumer) and pool relevant food groups
  - To analyze pooled samples for the selected contaminants
  - To multiply consumption data and the analytical data to estimate exposure to the contaminants

(Pennington and Hernandez 2002; Egan et al. 2007, Sirot et al 2009)

14

Examples of procedure for market basket survey

- Select representative foods for analysis
  - based on food consumption data to represent national typical diet
- Purchase food samples
  - In principle, for all food groups
  - considering the seasonal and regional variation

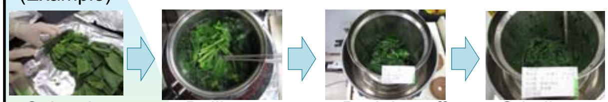
(examples of food groups)

15

Examples of procedure for market basket survey (for each food group)

- Preparation and grinding
  - For each food, grind after cooking as necessary

(Example)



Spinach Boiling Draining off Grinding

- Weighing, blending and homogenizing

- Analyze the pooled samples

16

Food groups for TDS

- As food consumption patterns vary across counties, food grouping for total diet study may be different

(Example of Japan)

- Uses 17 food groups and 1 group (drinking water)
- 17 groups >> 31 sub-groups >> 98 items

e.g. cereals and cereal products	e.g. wheat and wheat products	e.g. wheat floor; breads; noodles; pasta;

- based on the Japan's National Health and Nutrition Survey (annually conducted by MHLW)
  - classification for nutritional purposes
  - may not appropriate for the estimation of dietary exposure of contaminants

17

Analysis of the result

- For a target population (region, gender/age group),

A) Estimation of the intake from each food group
  - analytical result multiplied by consumption data divided by body weight of the population

B) Estimation of the total intake by summing of the intake from each food group

C) Estimation of the contribution of a food group to the total intake (the above A) divided by B))

- Some points for consideration
  - Values below LOD and LOQ in estimating mean occurrence (lower- and upper-bound approach)
  - Potential bias in population coverage in the consumption survey

18

Estimation of chronic (long-term) and acute (short-term) dietary intake

	long-term intake	short-term intake
Period	Lifetime	One day
chemical conc. in food	average/median	high percentile
Food consumption Data	average/median or high percentile of whole population	High percentile of eaters only
Target food	All the foods	Individual food
Tox reference values to compare with	PTDI, BMDL etc.	ARfD

19

Acute dietary exposure assessment

- Some substances could give rise to acute health effects in relation to short periods of intake
- JECFA and JMPR set an acute reference dose (ARfD) for such substances
- For pesticide residues, JMPR calculates the Internationally Estimated Short-term Daily Intake (IESTI) using:
  - 97.5th percentile consumption of food (eaters only) with
  - potentially highest concentration
- compare the IESTI with ARfD (general population, children <6 yr or women of child bearing age)

20

Acute dietary exposure assessment

- Several types of IESTI equations used by the JMPR depending on the unit size of a commodity
  - Case 1: unit weight < 25 g
  - Case 2: unit weight > 25 g
  - Case 3: processed commodity, bulked or blended

IESTI (mg/kg bw) = highest large portion (97.5th percentile of eaters) of the commodity (kg food per day) × median residue in a composite sample of edible portion (mg/kg) / mean body weight associated with the population for which the large portion was used (kg bw)

- For contaminants, JECFA set the group ARfD for deoxynivalenol (DON) and its acetylated metabolites
- High contribution of wheat to dietary intake of DON
  - The equation for the above Case 3 can be used

21

Whole population v.s. Eaters only

- Consumption data for the whole population of a food
  - include the consumption amount of “eaters” as well as “non-eaters” of that food
  - will generally be lower than the “eaters only” amount (i.e., the amount of food consumed only by those individuals who actually consumed the food)
- Consumption data for the “eaters only” of a food
  - used to estimate “worst-case” dietary exposure for high consumers

→ Check whether the consumption data to be used are based on “whole population” or “eaters only”

22

Uncertainty analysis in dietary exposure assessment

- Every dietary exposure assessment is associated with scientific uncertainties, which needs to be taken into account by risk managers
- Each uncertainty may be analyzed at one of 3 tiers: qualitative, deterministic or probabilistic
- Can be used to identify data gaps
- Procedure for qualitative analysis
  1. Identify sources and nature of uncertainty
  2. Give some indication of the direction (over- or under- estimate) and magnitude (high, medium, low) of each uncertainty on the assessment outcome
  3. Estimate the overall effect of the uncertainties

23

Uncertainty analysis in dietary exposure assessment

sources		examples
Exposure scenario		・target population ・target chemical ・target food(s) or food group(s)
Exposure model		・formula for calculation ・(for probabilistic approach,) fitted distributional curve
Model inputs	Conc. of chemicals	・sampling method ・No. of samples ・analytical method, quality control ・analytical results below LOQ
	consumption	(For dietary survey) ・method ・age ・No. of respondents ・survey period (and frequency)
	others	・body weight ・effect of processing/cooking ・types and amounts of raw ingredients

24

Comparison of the estimated dietary intake with toxicological reference values

25

Type of carcinogens

- Substances that induce cancer in experimental animals by non-genotoxic mechanisms
  - ➔ Considered to "have a threshold"
  - ➔ health-based guidance values can be established
- Substances that are both genotoxic and carcinogenic
  - ➔ generally considered to "have no threshold"
  - ➔ health-based guidance values cannot be established
  - ➔ Introduction of BMD, MOE approach, which provides a qualitative description of a possible prioritization of risks

26

Estimation of P(M)TDI

- No-observed-adverse-effect-level (NOAEL) or no-observed-effect-level (NOEL)

Safety factor (usually 100)

intra-species (10)
×
inter-species (10)

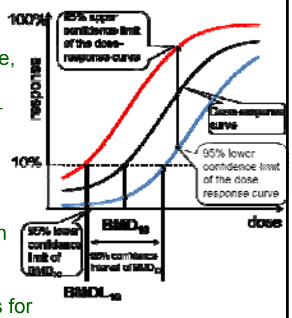
- P(M)TDI
  - permissible human exposure as a result of the natural occurrence of the substance in food

Instead of P(M)TDI, PTWI or PTMI is established depending on the properties of contaminants

27

BMD : Benchmark Dose

- BMD
  - Estimated from dose-response models of data
  - a dose producing a low but measurable adverse response, corresponding to a specified change in effect (generally 1–10%) over background
- BMDL
  - Lower bound 95 % confider limit of BMD
  - accounts for the uncertainty in the data
  - Enables determination of toxicological reference values for a substance without threshold



28

Margin of exposure (MOE) approach

- MOE = the dose causing a low but defined incidence of cancer (e.g. $BMDL_{10}$) / estimated human exposure
- MOE approach
  - provides advice to risk managers of how close estimates of human exposures are to those that produce a measurable effect in laboratory animals or humans
  - is used for both genotoxic carcinogens and non-genotoxic chemicals for which the database is not sufficient to set health-based guidance values
  - can be used for prioritizing chemical hazards for risk management actions

29

Implication of MOE

- For substances that are genotoxic and carcinogenic
  - MOE of 10,000 or higher (if it is based on the $BMDL_{10}$ from an animal carcinogenicity study)
  - ➔ low concern for public health
  - ➔ considered as a low priority for risk management actions
- For substances that are not genotoxic
  - MOE of 100 or higher
  - ➔ low concern for public health
- MOE only indicates a level of concern and does not quantify risk

30

Recent topics

31

Threshold of Toxicological Concern (TTC) approach

- The concept of TTC comes from "only the dose makes a poison"
- TTC approach
  - is a pragmatic screening and prioritization tool for the safety assessment of chemicals of unknown toxicity when the chemical structure is known and human exposure can be estimated
  - uses threshold values that represent life-long human exposure >> classified into 3 classes depending on chemical structure
    - Exposure below the corresponding threshold values is considered of low probability of adverse health effects
  - Enables efficient use of available resources

32

Establishment of TTC Value

- Division of a database of 613 chemicals into the three classes developed by Cramer et al, 1978
- Threshold values are calculated from the distribution of NOELs for each of the three classes (Munro et al, 1996)

Class I	Chemicals of simple structure, with efficient mode of metabolism suggesting low oral toxicity
Class II	Chemicals with structures less innocuous than Cramer Class I but without features suggesting significant toxicity
Class III	Chemicals with structures suggesting significant toxicity or which did not permit any strong initial presumption of safety

33

Summary

- Estimation of dietary intake
  - is an essential element for quantifying health risk
  - is used for prioritizing hazards, determining the necessity of risk management options, and verifying the effectiveness of the measures
  - requires food consumption data and concentration data of chemicals in food
  - requires the data based on the objectives and needs of risk management
  - uses as much data as possible

34

Summary

- Point estimation
  - is easy, not expensive, not time-consuming
  - does not show distribution of exposure
- Probabilistic estimation
  - provides the distribution of exposures
  - requires extensive data, PC and software
- Long-term exposure assessment
  - covers average (and if necessary, high-percentile) intake
- Short-term exposure assessment
  - covers high-percentile ("worst-case") intake
- Uncertainty analysis
  - can identify data gaps and serve as a basis for informed decision-making

35

Exercise 4 : Calculation of dietary exposure by point estimates

36

Exercise 4.1 : Exposure estimate based on occurrence data and food consumption data

- Concentration of chemical X in food Y: use the data in the Excel sheet "Ex.4 occurrence data"
- Consumption data of food Y (raw commodity) and Y_{p1}, Y_{p2}, a…

Food	Mean Consumption (whole population) (g/person/day)	Processing factor
Y	14.8	1
Y_{p1}	5.6	0.4
Y_{p2}	3.8	1.1
Y_{p3}	7.2	0.1

- Average body weight: 60 kg/person
- PTDI for chemical X : 0.3 μg/kg bw
- Calculate the following a) and b):
  a. Average long-term dietary intake (μg/kg bw/day)
  b. Percentage of the above intake to PTDI (%)

37

Solutions: Exercise 4.1

a. Average dietary intake (μg/kg bw/day)

Calculation based on median conc. of chemical X in food Y
(0.153 (mg/kg) × 14.8 (g/person/day)
+ 0.153 (mg/kg) × 0.4 × 5.6 (g/person/day)
+ 0.153 (mg/kg) × 1.1 × 3.8 (g/person/day)
+ 0.153 (mg/kg) × 0.1 × 7.2 (g/person/day)) / 60 (kg/person)
= 0.06 (μg/kg bw/day)

Calculation based on mean conc. of chemical X in food Y
(0.205 (mg/kg) × 14.8 (g/person/day)
+ 0.205 (mg/kg) × 0.4 × 5.6 (g/person/day)
+ 0.205 (mg/kg) × 1.1 × 3.8 (g/person/day)
+ 0.205 (mg/kg) × 0.1 × 7.2 (g/person/day)) / 60 (kg/person)
= 0.08 (μg/kg bw/day)

38

Solutions: Exercise 4.1

a. Percentage of the above intake to PTDI (%)

Calculation based on median conc. of chemical X in food Y
0.06 (μg/kg bw/day) / 0.3 (μg/kg bw)
= 19%

Calculation based on mean conc. of chemical X in food Y
0.08 (μg/kg bw/day) / 0.3 (μg/kg bw)
= 25%

39

Exercise 4.2 : Exposure estimate based on total diet studies

- Market basket study was carried out for chemical X for the general population in a country A.
- Analytical results (n =8) and consumption data for each food group is shown in next page and worksheet
- Average body weight: 60 kg/person
- Calculate the following a) and b)
  a. Average dietary intake (μg/kg bw/day)
  b. Contribution of the dietary intake from "fish and shellfishes" to the total dietary intake (%)

40

Food group	Mean analytical result (μg/kg)	Food consumption (g/person/day)
Cereals	3.7	439.7
Root and tuber vegetables	7.4	53.3
Other vegetables	1.5	268.1
Nuts and seeds	1.7	55.4
Edible fungi	0.9	16.8
Fruits	5.8	101.7
Algae	6.9	11.0
Fish and shellfishes	33.9	72.5
Meats	1.2	82.5
Eggs	6.5	34.8
Dairy products	1.7	117.3
Fats and oils	18.7	10.1
Confectionaries	8.9	25.1
Non-alcoholic beverages	1.3	598.5
Seasonings and condiments	2.2	87.0
Drinking water	0.3	2000

41

Solutions: Exercise 4.2

a. Calculation average dietary intake (total)
{3.7 (μg/kg) x 439.7 (g/person/day) + 3.7 (μg/kg) x 439.7 (g/person/day)
+ 1.5 (μg/kg) x 268.1 (g/person/day) + 1.7 (μg/kg) x 55.4 (g/person/day)
+ 0.9 (μg/kg) x 16.8 (g/person/day) + 5.8 (μg/kg) x 101.7 (g/person/day)
+ 6.9 (μg/kg) x 11 (g/person/day) + 33.9 (μg/kg) x 72.5 (g/person/day)
+ 1.2 (μg/kg) x 82.5 (g/person/day) + 6.5 (μg/kg) x 34.8 (g/person/day)
+ 1.7 (μg/kg) x 117.3 (g/person/day) + 18.7 (μg/kg) x 10.1 (g/person/day)
+ 8.9 (μg/kg) x 25.1 (g/person/day) + 1.3 (μg/kg) x 598.5 (g/person/day)
+ 2.2 (μg/kg) x 87 (g/person/day) + 0.3 (μg/kg) x 2,000 (g/person/day) }
/ 60 (kg/person)
= 0.14 (μg/kg bw/day)

b. Contribution of "fish and shellfishes" to the total exposure
33.9 (μg/kg) x 72.5 (g/person/day) / 60 (kg/person) / 0.14 (μg/kg bw/day) x 100 (%) = 30 (%)

42

Exercise 4.3 : Acute exposure estimate

- Food Y is a blended commodity
- Consumption data of food Y (raw commodity)
- Concentration of chemical XX in food Y: use the data in the Excel sheet "Ex.4 occurrence data"
- ARfD for chemical XX : 8 µg/kg bw

- Calculate the 99.9th percentile of short-term dietary intake (eaters only) of XX in food Y (µg/kg bw/day)
- Compare the estimated intake with the ARfD (%)

43

Solutions: Exercise 4.3

a. Calculation based on median conc. of chemical XX in Food Y

0.15 (mg/kg) × 321.5 (g/person/day) / 55.8 (kg/person)
= 0.86 (µg/kg bw/day)

derived from the values on the basis of kg food/person/day

Mean body weight of eaters

or

(0.15 (mg/kg) × 5.0 (g/kg bw/day)
= 0.75 (µg/kg bw/day))

derived from the values on the basis of kg food/kg bw/day

b. Percentage of the estimated intake to ARfD

0.86 (µg/kg bw/day) / 8 (µg/kg bw) × 100 (%)
= 11 (%)

or

(0.75 (µg/kg bw/day) / 8 (µg/kg bw) × 100 (%)
= 9.5 (%))

44

Exercise 4.4 : Consideration of uncertainty in point estimates

- Background information on both concentration data and food consumption data in Exercise 4.1 are provided in the next page and the Word file "Ex.4.4 Worksheet"

- List sources of uncertainty affecting the estimated dietary intake of chemical X as much as possible
- Indicate the direction (over- or under- estimate) of each uncertainty on the estimated dietary intake

45

Exercise 4.4 Background information on concentration data

- Surveillance of chemical X in domestically produced foods (food Y and its processed commodities as mentioned in Exercise 4.1) was conducted in country A in 2013.
- Samples were collected in 2013 and stored at -20 degree Celsius until analysis in 2015.
- 80% of chemical X was retained during storage for 2 years at -20 degree Celsius, according to the storage stability study.
- Concentrations of X are known to vary greatly from year to year.
- Food Y: 40% domestically produced, 60% imported
- While food Y is produced throughout country A, samples were collected only from eastern part of the country
- Analyte: chemical X only
- JECFA established the group PTDI for chemical X and its metabolite X_m (expressed as X).

46

Exercise 4.4 Background information on food consumption data

- Food consumption survey was conducted throughout country A, in a total of 25 cities from 2005 to 2007
- The survey was conducted by 24h dietary recall
- The survey covered only one season (dry season) per year, while there is another season (rainy season) in country A.
- The survey covered three independent weekdays for each subject (individual).
- Total number of subjects: 9,510 (>1yr), 227 (1 - 6 yr)
- Total number of participating person days: 24,389

47

Well done !!!

48