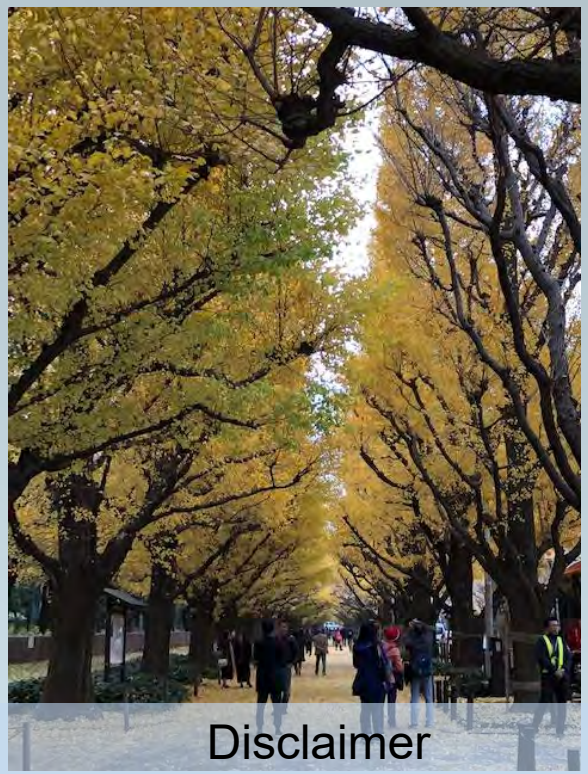
FAO Regional Training Workshop Enhancing Effective Participation in Codex Activities: Developing science-based national positions and contributing scientific data to the Codex standard-setting activities
Tokyo, Japan, 5-7 December 2018

Toxicological evaluation of pesticide residues at JMPR, the scientific advisor of CCPR



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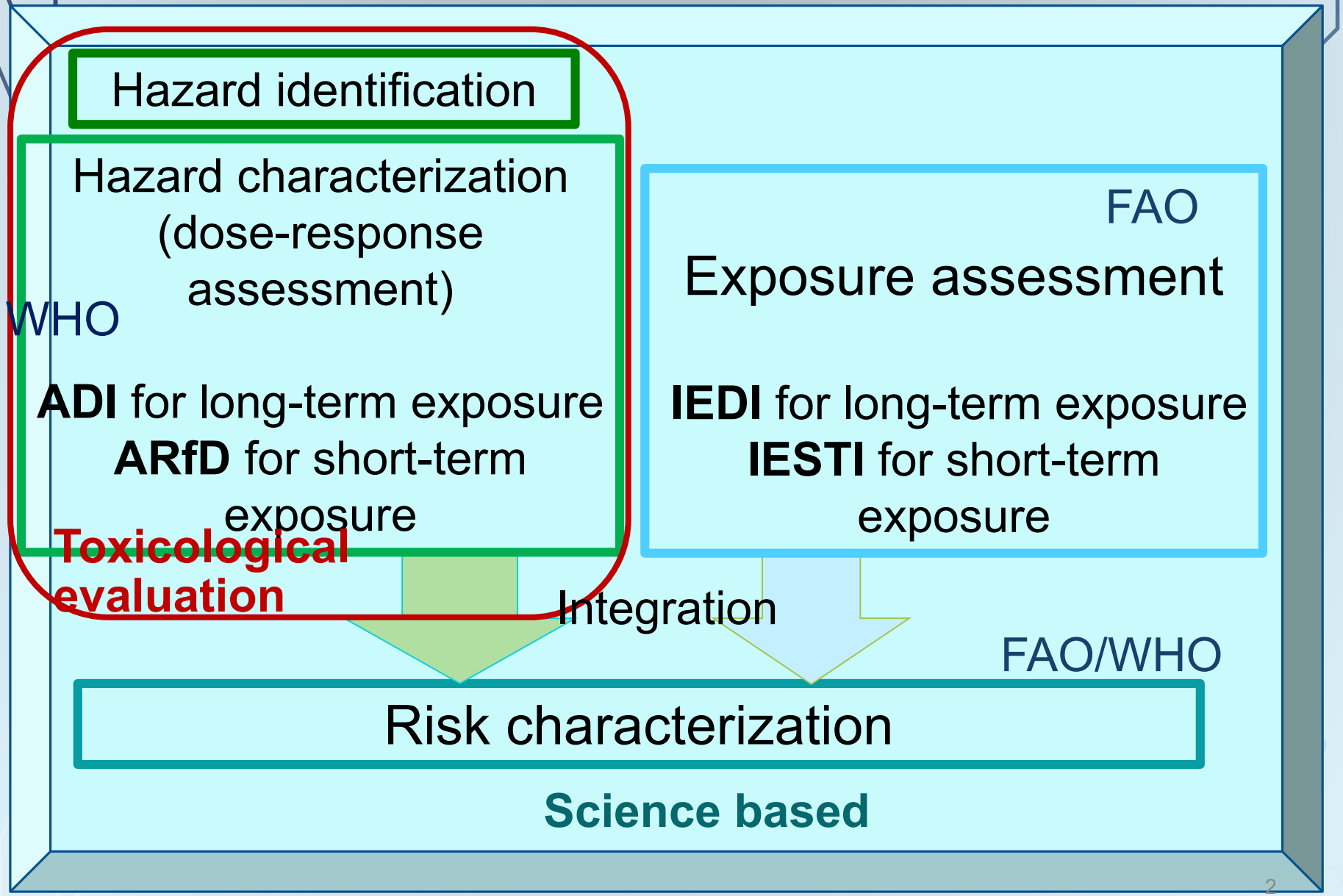
Disclaimer

The views, thoughts and opinions presented are not necessarily those of JMPR

Four steps in risk assessment



WHO/FAO, 2009: IPCS EHC240 Principles and Methods for the Risk Assessment of Chemicals in Food

Outlines:

1. What is toxicity ?
2. Purpose of toxicological evaluation
   HBGVs (ADI/ARfD)
3. Key points of toxicological evaluation
   - Who is evaluating how toxicity? -
   a. Data quality
   b. Setting ADI/ARfD
4. Current topics
   Evaluation of metabolites

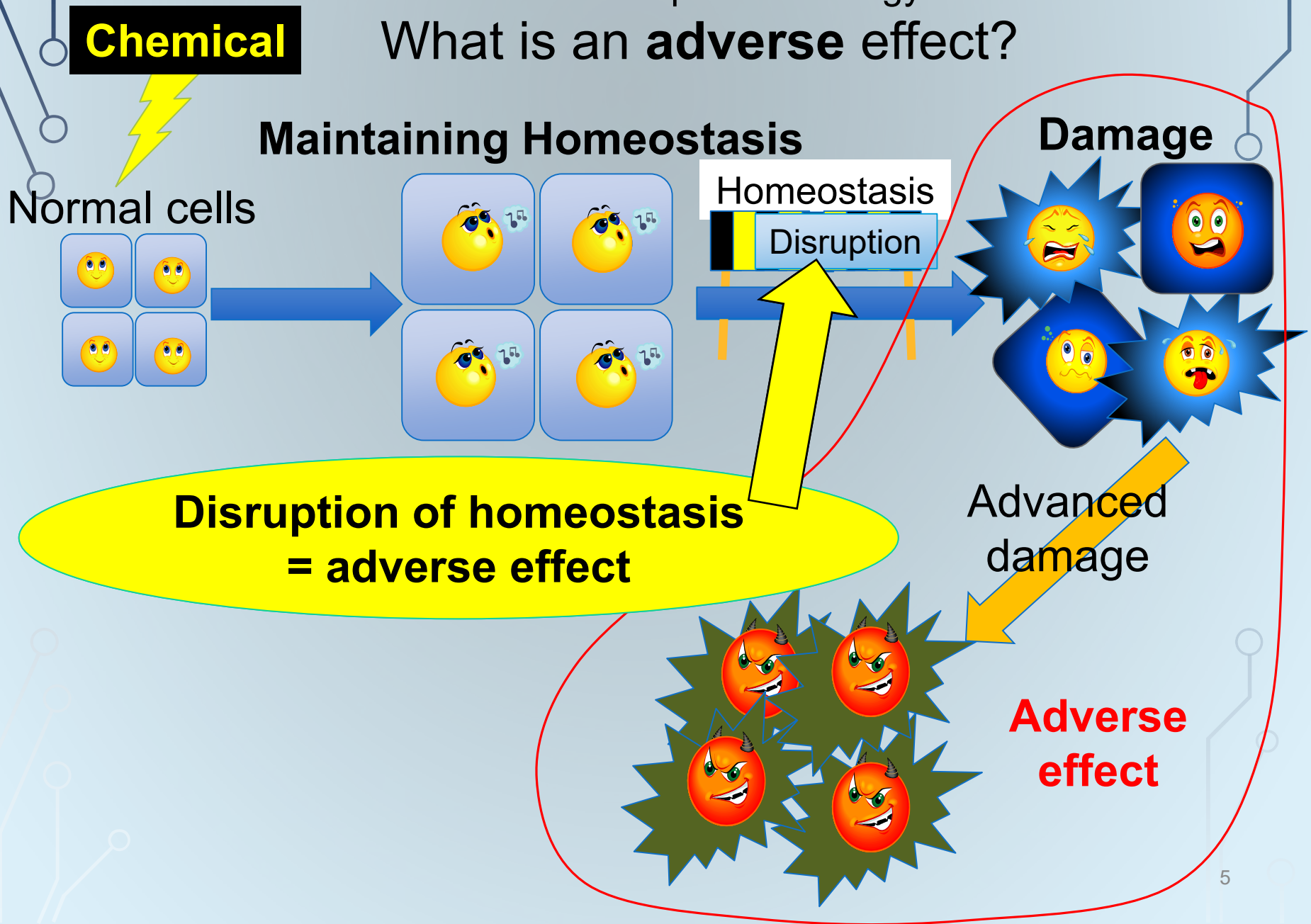
Dr. Keyword

1. What is toxicity

- Adverse effect
- In the dietary risk assessment of pesticides, the target is human health

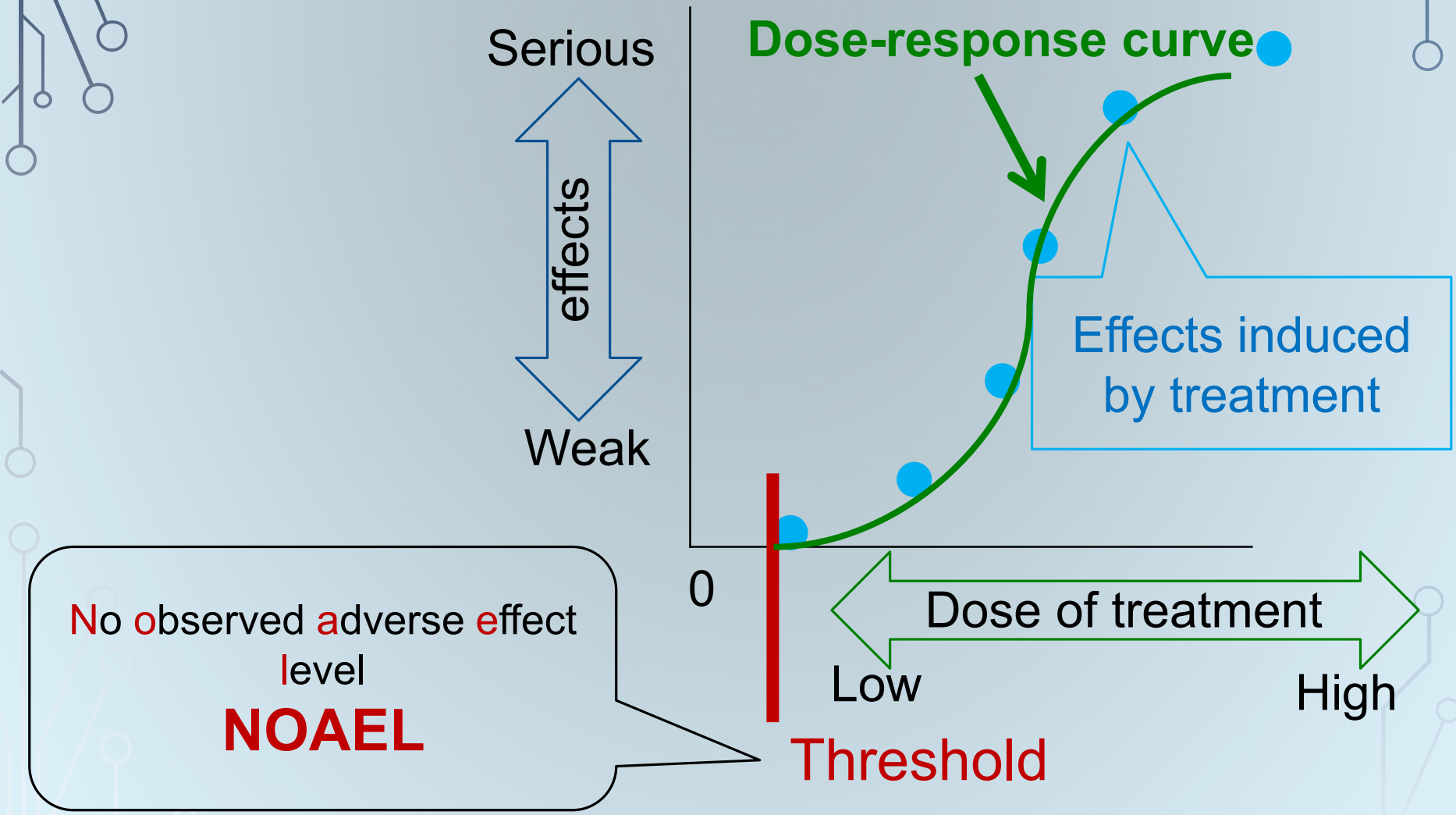
Basic concept of toxicology:

What is an **adverse** effect?



Basic concept of toxicology:

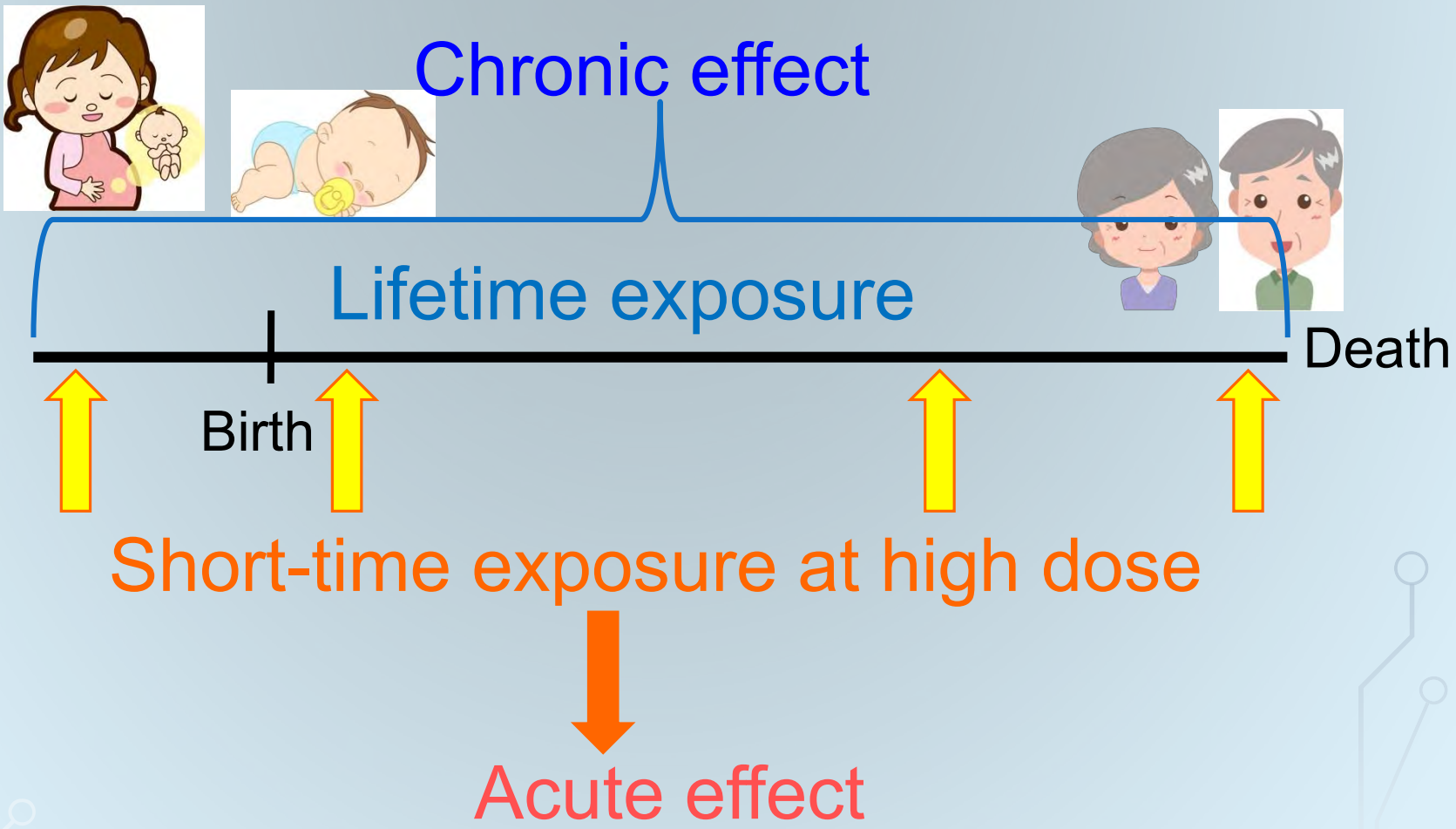
Threshold in Dose-response relationship



2. Purpose of toxicological evaluation

To find adverse effect induced by a chemical
and
to find a level of no adverse effect

Two types of adverse health effect on humans



Purpose 1

To set health guidance value for chronic effect

1. Acceptable Daily Intake (ADI) :

Definition

The amount of pesticide to which human can be exposed daily **for a lifetime** without injury

Purpose 2

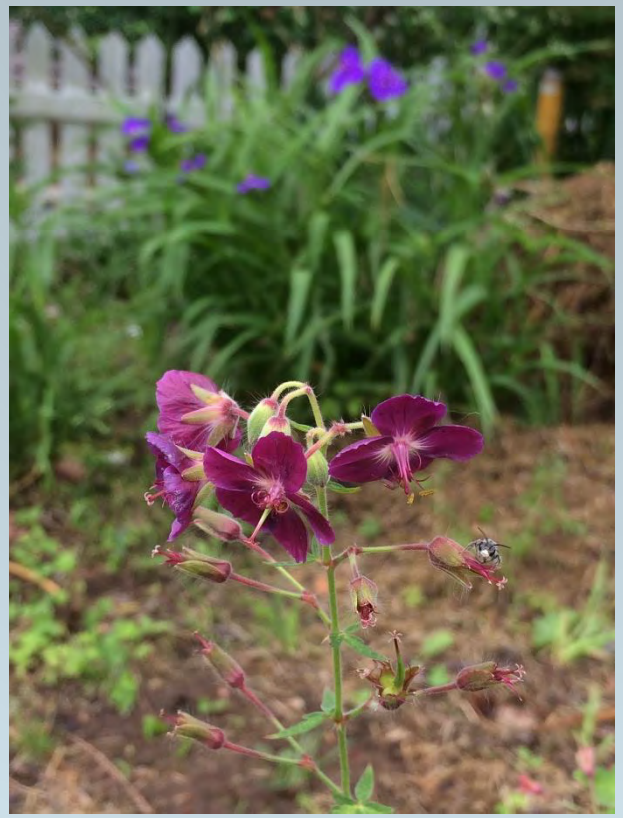
To specify a health guidance value for acute effect

2.Acute Reference Dose (ARfD) :

Definition

The amount of pesticide that can be ingested **in a period 24 hours or less** without injury

3. Key points of toxicological evaluation
- How is toxicity evaluated by Who? -



Toxicology data

Acute toxicity

Reproductive

Repeated toxicity

Genotoxicity

TK, MOA

Carcinogenicity

GLP

Test guidelines

Identified/Compiled toxicity profiles/
Find endpoints for threshold

Who?

Risk assessors with expertise of toxicology

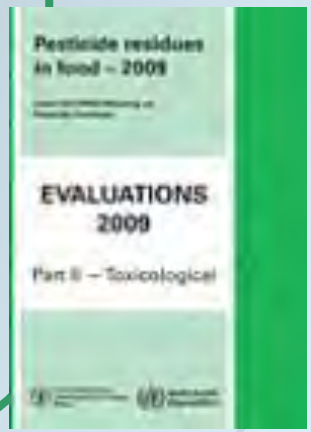
Threshold (NOAELs)

Chronic

Acute

ADI

ARfD



Documented in summary/monograph

How? Toxicological evaluation process at JMPR

Data necessary for toxicological evaluations of pesticides at JMPR

- Basic data
  - ✓ Acute toxicity
  - ✓ Short-term toxicity
  - ✓ Long-term toxicity/carcinogenicity
  - ✓ Genotoxicity
  - ✓ Reproductive toxicity
  - ✓ Teratogenicity

Rat

Mice

- Useful data

  Neurotoxicity, Immunotoxicity, Mechanism of toxicity

  Toxicity of metabolite/degradate

  Irritation/sensitivity

  Kinetics (absorption/distribution/metabolism/excretion)

  Human data

3. Key points of toxicological evaluation
a. Quality of data

Why is quality of data important?

Evaluate with
- ✓ Robustness
- ✓ Transparency
- ✓ Consistency

What is principle(s) to control quality of data?

1. Toxicity study conducted in compliant with **G**ood **L**aboratory **P**ractice, **GLP**
2. Toxicity study conducted in accordance with **authorized test-guideline** nationally/internationally

Good Laboratory Practice

Quality system of management controls for research laboratories and organizations

to ensure the **uniformity, consistency, reliability, and reproducibility** of chemical in non-clinical safety studies

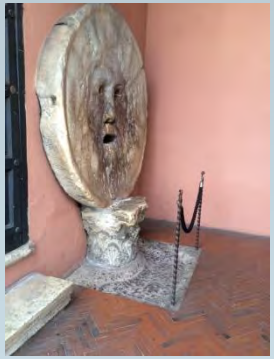
GLP embodies a set of principles that provides a **framework within which laboratory studies** should be planned, performed, monitored, recorded, reported and archived.

Test Guidelines (TG)

A set of accepted **specifications for the testing** of chemicals by national/international authorities

Global standard

OECD* test-guidelines



GLP spirit = To be honest

OECD*, Organization for Economic Co-operation and Development

3. Key points of toxicological evaluation
b. Setting ADI/ARfD

After identified and compiled toxicological profiles of a pesticide,
assessors specify **N**o **O**bserved **A**dverse **E**ffect **L**evel,
NOAEL in each toxicity study
based on the toxicological endpoint(s)
at **L**owest **O**bserved **A**dverse **E**ffect **L**evel, **LOAEL**

Endpoint:
A finding induced by the treatment observed at LOAEL.
Ex) Inhibition of acetylcholine esterase (AchE) activity is sensitive endpoint of organophosphorus/carbamate.

How to set NOAEL/LOAEL

Assessors determine NOAEL based on endpoints at lowest dose detected toxicity/adverse effect

In short-term toxicity study in rats

Dose tested	Toxicity/adverse effect
100 mg/kg bw	✓ Hepatocellular necrosis ✓ Anemia ✓ Body weight decrease
20 mg/kg bw	✓ Body weight decrease
5 mg/kg bw	✓ No effect

Adverse effects

Endpoint to set NOAEL

LOAEL

NOAEL

LOAEL, Lowest observed adverse effect level
NOAEL, No observed adverse effect level

ADI setting for lifetime exposure without adverse health effect

Various toxicity studies

↓

The lowest NOAEL
in the most sensitive species
(mg/kg bw/day)

/safety factor = Usually 100

↓

ADI mg/kg bw(range)

Example） 2-year chronic/carcinogenicity study in rats

1.35 mg/kg bw/day

↓

0-0.013 mg/kg bw

Uncertainties

Human is hypothesized as the most sensitive species

100 as a safety factor

ARfD
for exposure within 24 hours or less

Toxicology data

Common process

Toxicity profiles

Evaluation

NOAELs/LOAELs

Different point of view

Chronic

Acute

ADI

ARfD

Choose the lowest NOAEL in all studies

Toxicological evaluation process

ARfD setting is necessary or not?

- High acute toxicity?
- Any toxicities found within single or a few day after treatment ?
- Teratogenicity?
- Local effect?

ARfD setting
Stepwise process 2

The lowest NOAEL after single dose exposure (mg/kg bw/day)

/Safety factor = Usually 100

ARfD mg/kg bw (value)

Example）Acute neurotoxicty study in rats (single dose exposure)

20 mg/kg bw

0.2 mg/kg bw

ARfD>=ADI

Uncertainty

Human is hypothesized as the most sensitive species

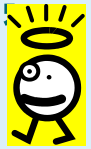
100 as a safety factor

4. Current topics
Evaluation of metabolites

Why are metabolites important in risk assessment ?

- Consumers are exposed to pesticides via plants or livestock feeding plants
- Metabolites and their concentrations might be different between not only species but also in edible tissues
- Specific metabolites in plants

What and Why is ’ Threshold of Toxicological Concern, TTC approach?



- **Adequate data of metabolites**

  Fine

- **Toxicity data are lacking**

On the basis of concept that **only dose makes that a thing is no poison**, the amount of intake is no concern for human health **if the intake of metabolite is very small.**

The amount of intakes is classified into 3 classes by chemical structure.

Key studies for TTC

Study 1: Cramer et al. (1978)

Division of the database of 613 chemicals into the three classes

- **Class I:** Simple structure, 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**

Key studies for TTC

Study 2. Munro (1996)
Analysis of 5 percentile of the cumulative distribution of **NOEL**s of 613 chemicals using Cramer's criteria, and establishment of TTC values

TTC value = 5%ile NOEL/100

Cramer Class	Number of chemicals	5%ile NOEL (mg/kg bw/day)	TTC value (μg/kg bw/day)	(μg/person/day)
I	137	3.0	30	1800
II	28	0.91	9	540
III	448	0.15	1.5	90

Person, 60 kg body weight

TTC approach at JMPR (WHO, 2015)

17 steps using the flow-chart

Step 1-5: Comparison of metabolite toxicity with parent using toxicity data

Step 6-11: Genotoxic potential (Direct damage to DNA):
Threshold, 0.0025 μg/kg bw/day (0.15 μg/person/day)

Step 11: Organophosphate/carbamate(Seriously toxic but not genotoxic):
Threshold, 0.3 μg/kg bw/day (18 μg/person/day)

Step 12-17: Classification by the amount of intake and chemical structure

- Cramer Class I: 1800 μg/person/day (30 μg/kg bw/day)
- Cramer Class II: 540 μg/person/day (9 μg/kg bw/day)
- Cramer Class III: 90 μg/person/day (1.5 μg/kg bw/day)

Other non-testing method in metabolite evaluation

- Read-across
- (Q) SAR

Concept of toxicology

All things are poison and nothing is without poison; only **the dose makes that a thing is no poison**.

Paracelsus (1493-1541)

Please enjoy following lecture by Dr. Yukiko Yamada

Thank you so much for your attention

Principles and Guidance published by FAO/ WHO

- IPCS (2009) Environmental Health Criteria 240. Principles and Methods for the Risk Assessment of Chemicals in Food. http://www.who.int/foodsafety/publications/chemical-food/en/
- World Health Organization (2015) Pesticide residues in food. WHO Core Assessment Group on Pesticide Residues. Guidance document for WHO monographers and reviewers http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr_Guidance_Document_FINAL.pdf?ua=1

Reference of toxicological concern for animal/plant metabolites

- Cramer GM, Ford RA, Hall RL. (1978), Estimation of toxic hazard – a decision tree approach. Food Chem Toxicol. 16: 255–276.
- Munro IC, Kennepohl E, Kroes R. (1996),. Procedure for the safety evaluation of flavouring substances. Food Chem Toxicol. 37:A 207–232
- Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Würtzen G. (2004), Structurebased thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol. 42: 65–83.

Reference of toxicological evaluation process and current topics

- Hamilton D, Yoshida M, Wolterink G, Solecki R. Evaluation of pesticide residues by FAO/WHO JMPR in Food Safety Assessment of Pesticides Residues (Eds. Ambrus A & Hamilton D) pp. 113- 196. 2017 World Scientific. New Jersey