State of the Science Conference on Pesticides and Cancer
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TOXICOLOGY OF PESTICIDES, THE SCIENCE OF RISK ASSESSMENTS AND INTERNATIONAL STANDARD SETTING

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Outline

- **Joint FAO/WHO Meeting on Pesticide Residues (JMPR)**
- **Risk assessment of pesticides**
  - Hazard characterisation (ADI; ARfD)
  - Residue evaluation (MRL, ….)
  - Dietary exposure assessment
- **Refinements, Challenges and Perspectives**

JMPR: the history (1)

1961: Recommendation to DG of FAO and WHO to evaluate pesticide residues

1963: First JMPR convened to establish ADIs, annual meetings ever since

1966: First meeting to consider both ADIs and MRLs

Who is in JMPR?

Committee is selected for each meeting:

- **<u>Drafting experts</u>: assess available data and prepare draft working paper for discussion at the meeting, participate in meeting and contribute in discussions**
  - FAO: *Consultants*
  - WHO: *Temporary Advisers*
- **<u>Members</u>: invited by FAO (Panel of Experts) and WHO (Core Assessment Group), are responsible for conclusions and adoption of report (Chairman, Vice-Chairman, two rapporteurs)**
- **Drafting Experts and Members belong to Regulatory Bodies, Academia or Research Institutes**

Joint FAO/WHO Secretariat of JMPR

JMPR: the history (2)

1990: Principles for the Toxicological Assessment of Pesticide Residues in Food (EHC 104), now under revision

1995: Consideration of acute toxicity (acute reference dose)

2004: Pilot project for Worksharing - trifloxystrobin

2005: Guidance document published on the setting of ARfDs

2008: Consideration of a pilot project to recommended MRLs prior to National Government Registrations

JMPR Output

Summary Report:

➔ **Electronic summary containing only basic conclusions**

Report:

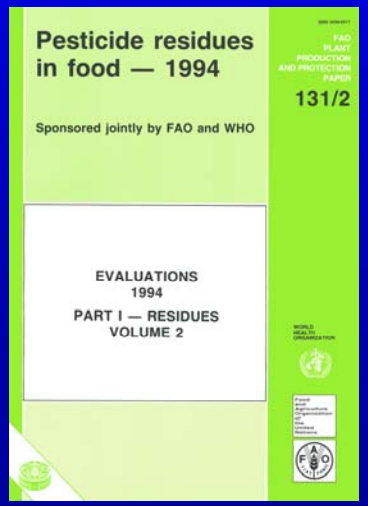
➔ **Concise summary of relevant information for evaluation and conclusion, including intake estimates**

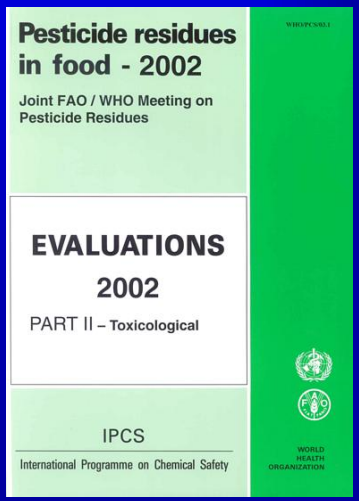
Monographs:

➔ **Detailed description and evaluation of all available data used in evaluation**

(1) Toxicological Monographs

(2) Residue Monographs (MRLs etc.)





JMPR Output

To date evaluated:

- **Over 250 pesticides**

JMPR at WHO:

http://www.who.int/pcs/food/jmpr/en/

JMPR at FAO:

http://www.fao.org/ag/agp/agpp/Pesticide/Default.htm

JMPR and International Food Safety Standards

- JMPR assessments feed directly into international standard setting via the Codex Alimentarius Commission
- Codex Standards are an integral legal part in international food trade (WTO-SPS)

JMPR
JECFA
JEMRA

CCPR
CCCF
CCFA
CCRVDF
CCFH

Toxicological Hazard Characterization

Data sources

- **Data developed by manufacturers**
- **Open scientific literature**

Types of data

- **Biochemical data**
  - Absorption, distribution, excretion, metabolism, effects on enzymes
- **Toxicological data**

Toxicological Hazard Characterization

➔ **Toxicological data**

- **Acute, short-term, long-term toxicity & carcinogenicity**
- **Genotoxicity**
- **Reproductive toxicity**
- **Special studies (e.g. immunotoxicity, neurotoxicity, cardiovascular effects, thyroid function)**

➔ **Studies on metabolites**

➔ **Observations in humans**

Toxicological Hazard Characterization

Assessment

- ➔ **Identification of critical toxicity endpoint and critical study**
- ➔ **Identification of the No Observed Adverse Effect Level (NOAEL)**
- ➔ **Identification of appropriate uncertainty/safety factors**
- ➔ **Derivation of reference value by dividing NOAEL by uncertainty factor**

Taking overall database into account (weight-of-evidence approach)

Outcome

ADI – acceptable daily intake

ARfD – acute reference dose

Outcome: Health-based Guidance Values

ADI – estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk. (WHO 1987)

ARfD – estimate of the amount of a substance in food and/or drinking water, expressed on a body-weight basis, that can be ingested in a period of 24h or less without appreciable risk to the consumer on the basis of all known facts at the time of evaluation. (JMPR 2002)

Residue Evaluation – Data

- Chemistry
- Metabolism
- Analytical methods and freezer storage stability
- Good agricultural practice
- Supervised residue trials
- Food processing
- Livestock feeding studies
- External animal treatments
- Residue definition

Residue Evaluation – Outcome

- **Residue definition:**
  - Relevant for risk assessment
  - Relevant for monitoring
- **Maximum Residue Level (MRL)**
  - Proposed standard for agricultural commodity
- **Standard Trial Median Residue (STMR):**
  - Used in chronic dietary exposure assessment
- **High Residue Level (HR):**
  - Used in short-term dietary exposure assessment

Dietary Exposure Assessment

Exposure = chemical concentration x food consumption

Chronic - Daily over life time

Acute - within 24h or less

Estimated intake < ADI/ARfD = MRL recommended

Estimated intake > ADI/ARfD = MRL recommended with precautionary statement for consideration by CCPR and MS

REFINEMENTS, CHALLENGES AND PERSPECTIVES

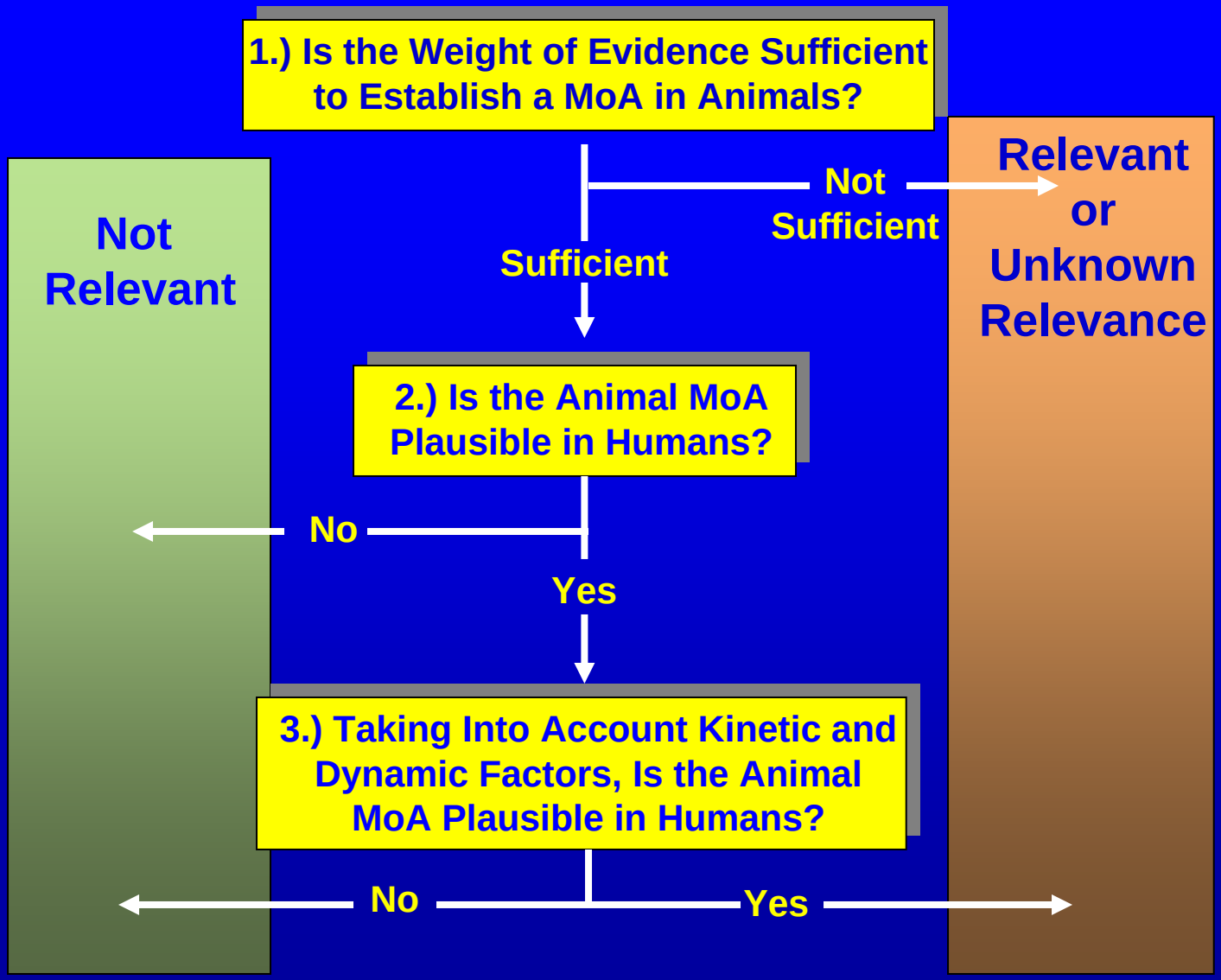
REFINEMENTS

- **Cancer mode of action framework**
- Inhibition of acetylcholinesterase vs plasma cholinesterase after exposure to organophosphate or carbamates
- Use of human data
- Thyroid effects in rats and their relevance in human risk assessment
- Liver toxicity
- Local *vs* systemic effects

Standard sentences used by JMPR when evaluating carcinogenic risk of pesticides

- Because [. . . . . .], the Meeting concluded that [pesticide name] is unlikely to pose a carcinogenic risk to humans
- The Meeting concluded that the increased incidence of tumours observed in [organ or tissue] was a threshold phenomenon, that was species- and sex-specific, and that [pesticide name] was therefore unlikely to pose a carcinogenic risk to humans
- In view of the lack of genotoxicity and the finding of tumours only in mice and only at concentrations at which severe toxicity was observed, the Meeting concluded that [pesticide name] is not likely to pose a carcinogenic risk to humans

Framework Analysis of Cancer MOA



Assessment of the carcinogenic potential of pesticides evaluated by JMPR (1998-2007)

(compounds evaluated = 82) None found to pose genotoxic risk

No evidence of carcinogenicity in animals (and humans)	58
Carcinogenic effect in animals at the highest dose tested	
Equivocal	4
Associated with systemic toxicity	6
Carcinogenic effects in animal via a mechanism not relevant to human	9
Species and/or sex specific effects, not relevant to humans	5

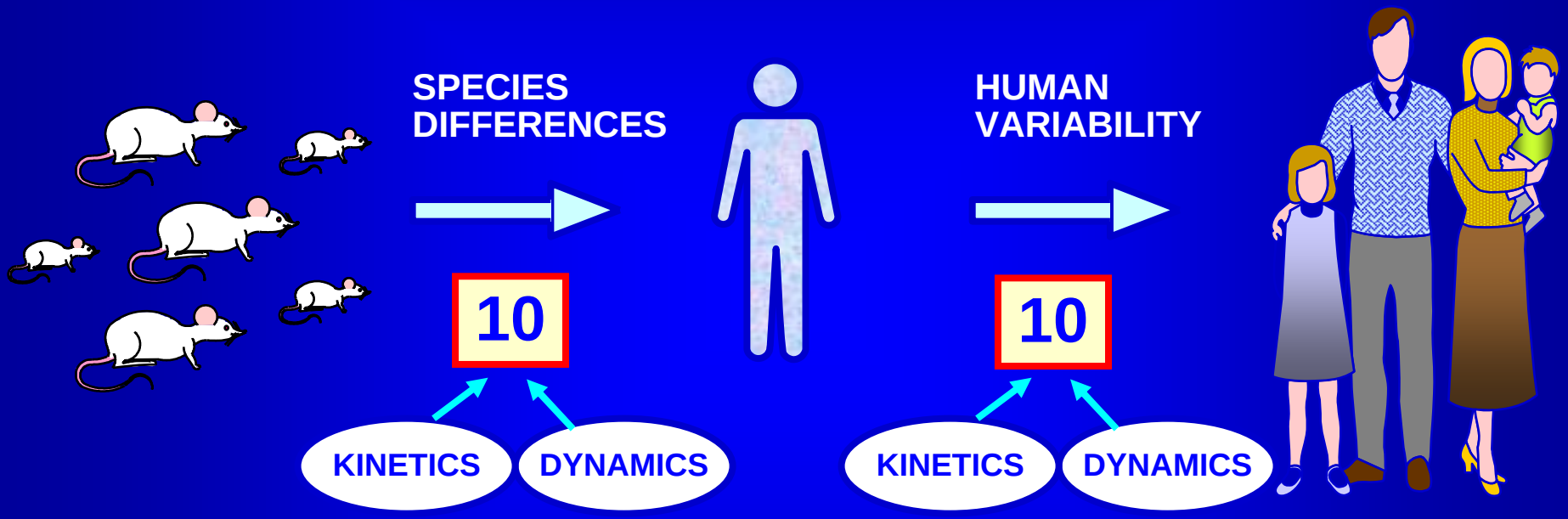
In total 82/82 compounds were considered unlikely to pose a carcinogenic with to humans

Challenges

- **Uncertainty factors**
- **Dose-response in modeling**

Default Uncertainty Factors

The usual 100-fold uncertainty factor includes two 10-fold factors for species differences and human variability



The 10-fold interspecies factor allows for both toxicokinetics and toxicodynamics

Use of Chemical Specific Adjustment Factors

- **Interspecies difference = 10**
  - Toxicodynamic = 2.5
  - Toxicokinetic = 4.0
- **Intraspecies difference = 10**
  - Toxicodynamic = 3.3
  - Toxicokinetic = 3.3

Dose Response Modeling

General issues

- **Extrapolation from toxicity in experimental systems at exposures typically significantly higher than human exposure**
- **Use of mathematical and statistical methods increasing, but lack of agreed upon approaches for Dose-Response modeling**
- **Every model only as good as the data ('garbage in – garbage out')**

Dose Response Modelling

Applicability

➔ **Point of departure for 'safety assessment'**

- BMD and BMDL versus NOAEL , i.e. modeling in the observable range

➔ **Low dose extrapolation**

- Linear from PoD (reference point)
- Low dose modeling – quantitative risk assessment (upper bound)

Perspectives

- **Updating food consumption databases**
- **High/special consumers**
- **Probabilistic *vs* point estimates**
- **Physicologically Based Toxicokinetic Modeling**

Concluding Remarks

- **Risk assessment of pesticides follows a systematic approach taking the overall weight-of-evidence of the data into account**
- **Science (data)-based approaches take precedence over default approaches**
- **Current system to evaluate pesticides on the international level is aimed at global public health protection**