METHODOLOGY

CONTAM Opinion on dioxins and DL-PCBs in food and feed

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efsa
European Food Safety Authority

Methodology

Selected as pilot opinion to implement the principles of the Prometheus framework

PROmoting **METH**ods for **E**vidence **U**se in **S**cience

Methodology

PROmoting **METH**ods for **E**vidence **U**se in **S**cience

Contribute to:

- **further develop and improve** the methods for dealing with evidence in EFSA scientific assessments
- **increase consistency** of these methods in EFSA
- **increase Transparency and Openness** of EFSA scientific outputs

Methodology

PROmoting **METH**ods for **E**vidence **U**se in **S**cience

Consist of:

- ✓ **Develop a priori the strategy** of the Risk Assessment (RA)
- ✓ **Perform** each step of the RA in line with the strategy
- ✓ **Document** the process
- ✓ **Document any refinements/changes**

The strategy: initial considerations

- Evidence on all 29 target congeners (17 PCDD/Fs and 12 DL-PCBs)
- Both animal and human data to derive a reference point
- For the human risk assessment, the SCF (2000, 2001) assessments were taken as starting point
- Focus on adverse effects observed at low levels of exposure
- Application of the WHO_{2005}-TEFs (uncertainties known)
- Use of a body burden approach rather than one based on external dose

The strategy: the process

Translate the terms of reference into **sub-questions**

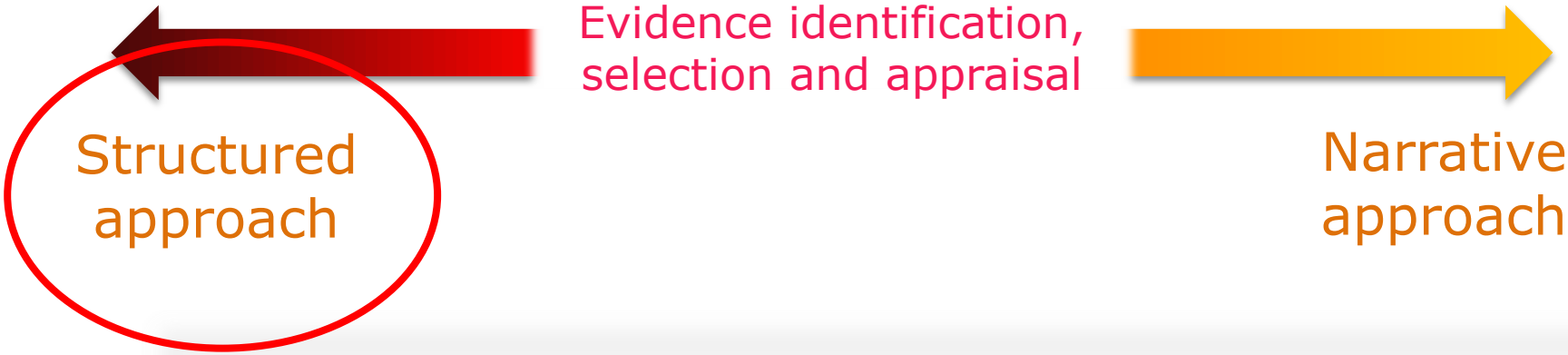
The scientific opinion should, *inter alia*, comprise the:

a) evaluation of the toxicity of dioxins and dioxin-like PCBs for animals and humans, considering all relevant adverse acute and chronic health effects;

- ***What adverse outcomes are associated with*** *exposure to PCDD/Fs and DL-PCBs in* ***humans****?*
- ***Which adverse outcomes occur*** *following exposure to PCDD/Fs and DL-PCBs in* ***experimental animals*** *at body burdens measured/estimated to be <100 ng TEQ/kg bw?*
- *Are PCDD/Fs and DL-PCBs* ***genotoxic****?*
- *What is the* ***ADME*** *of the target compounds in humans?*

The strategy: the process

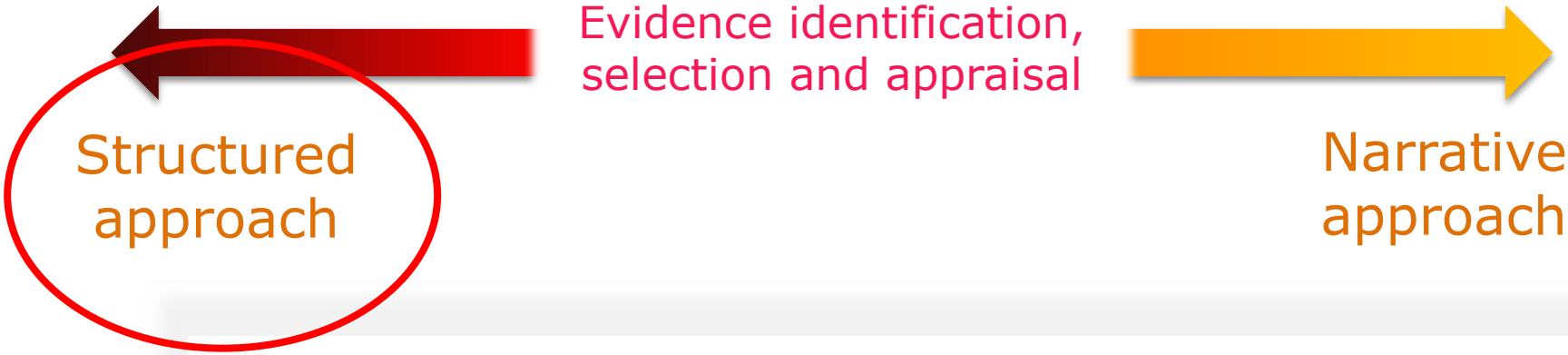
Select the **approach to answer each sub-question**



- **Extensive literature search** (ELS)
- Selection with **inclusion/exclusion criteria**
- Structured **appraisal** (risk of bias – NTP OHAT based)
- Structured **synthesis** of the evidence (tables)

The strategy: the process

Select the **approach to answer each sub-question**



- *What are the **adverse outcomes** in **humans**?*
- *What are the **adverse outcomes** in **experimental animals**?*
- *What are the **adverse outcomes** in **farm/companion animals**?*

The strategy: the process

Structured approach

Epidemiological studies

In	All endpoints, including hormone levels
Out	Studies on gene expression only Studies on drug metabolising enzyme activity/levels only

Studies in experimental animals

In	All endpoints
Out	Studies on enzyme induction only (e.g. CYP modulation) Studies on gene expression only Studies on co-administration of pro-carcinogens (CON A, DMBA, NKK) only Studies on -omics profiles Studies on the protective effects of certain substances against PCDD/Fs and/or DL-PCB toxicity

The strategy: the process

Structured approach

Epidemiological studies

- Only studies in which the **levels of the compounds in tissues** have been measured

- TCDD or any other congener dominating the TEQ
- 17 PCDD/Fs and 12 DL-PCBs,
- 17 PCDD/Fs and 4 non-*ortho* DL-PCBs,
- 17 PCDD/Fs and 3 non-*ortho* DL-PCBs (including PCB-126),
- Total TEQs (or BEQs by, e.g. CALUX).

Studies in experimental animals

- Only studies in which the administration of the target compounds included measured/estimated **body burdens <100 ng TEQ/kg bw**

- Only those in which **TCDD** alone was administered

The strategy: the process

Structured approach

Epidemiological studies

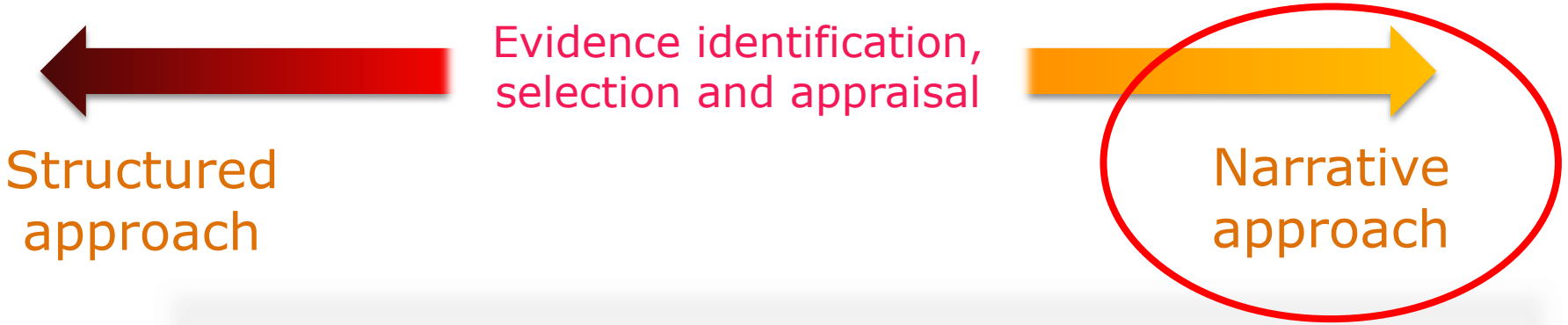
- ✓ Extensive Literature Search: **6,101**
- ✓ Selection for relevance: **257**
- ✓ Further selection + update search: **198** (appraised)

Studies in experimental animals

- ✓ Extensive Literature search: **4,921**
- ✓ Selection for relevance: **272**
- ✓ Further selection + update search: **17** (appraised)

The strategy: the process

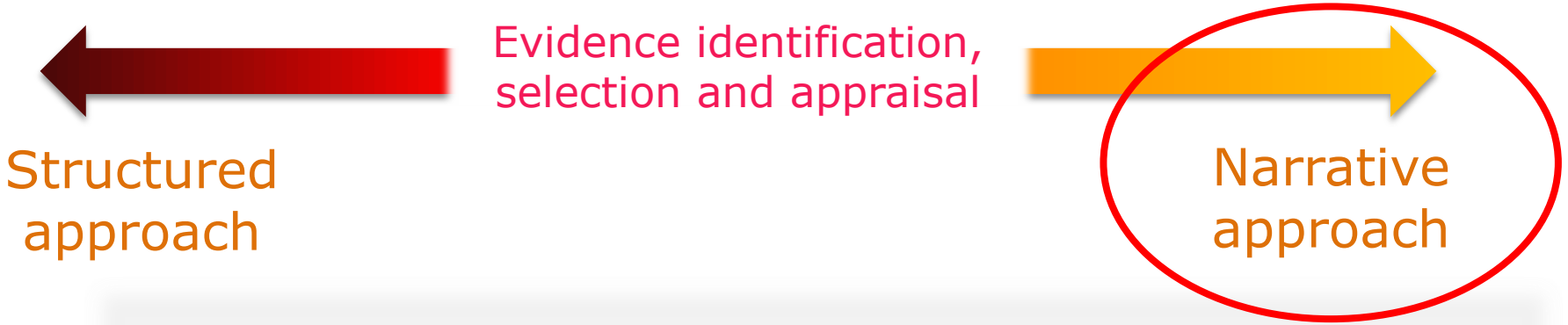
Select the **approach to answer each sub-question**



- Literature search to identify relevant reviews, systematic reviews, meta-analysis or papers.
- Screened and evaluated by relevant domain experts from the Working Group.

The strategy: the process

Select the **approach to answer each sub-question**

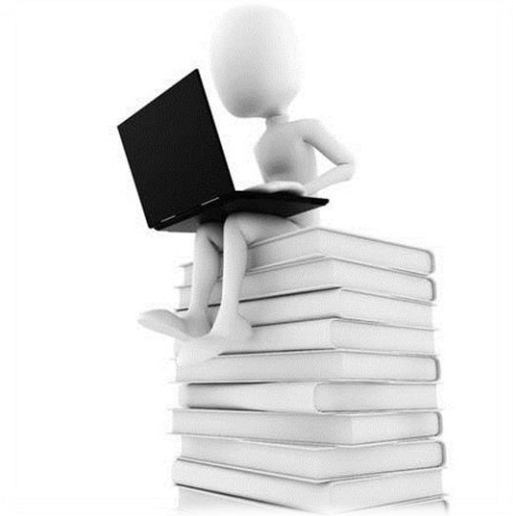


- *Are PCDD/Fs and DL-PCBs **genotoxic**?*
- *What **molecular mechanisms** can explain the observed adverse effects?*
- *What is the **effect of processing** on the levels in food?*

The strategy: the process

Assess the **reliability of the studies**

- Considering the **risk of bias**, defined as 'the extent to which the design and conduct of a study are likely to have prevented bias', i.e. non-random error.
- **Critical appraisal tools** (series of questions) developed by tailoring the NTP-OHAT Risk of Bias Tool (Rooney et al., 2014).



Confounding bias:
Did the study design or analysis account for important confounding and modifying variables?

Detection bias:
Can we be confident in the exposure characterisation?

…

The strategy: the process

Assess the **reliability of the studies**

Expert judgement was translated into a rating scale for each question:

[**++**]: definitely low risk of bias
[**+**]: probably low risk of bias
[**-**]: probably high risk of bias
[**- -**]: definitively high risk of bias

The individual rating for each question was translated to an **overall tier of reliability** for each individual study:

Tier 1 - low risk of bias
Tier 2 - moderate risk of bias
Tier 3 - high risk of bias

The strategy: the process

Evaluate the confidence in the body of evidence

Considering: e.g. the presence of effects at low doses, and other factors that can decrease or increase the confidence in the evidence

Integrate the lines of evidence

Identification of critical endpoints from both human and experimental animal lines of evidence considering the respective level of confidence.

Method to **perform** hazard characterisation

Dose-response assessment on relevant adverse effects for the identification of reference points (e.g. a NOAEL or BMD/BMDL).

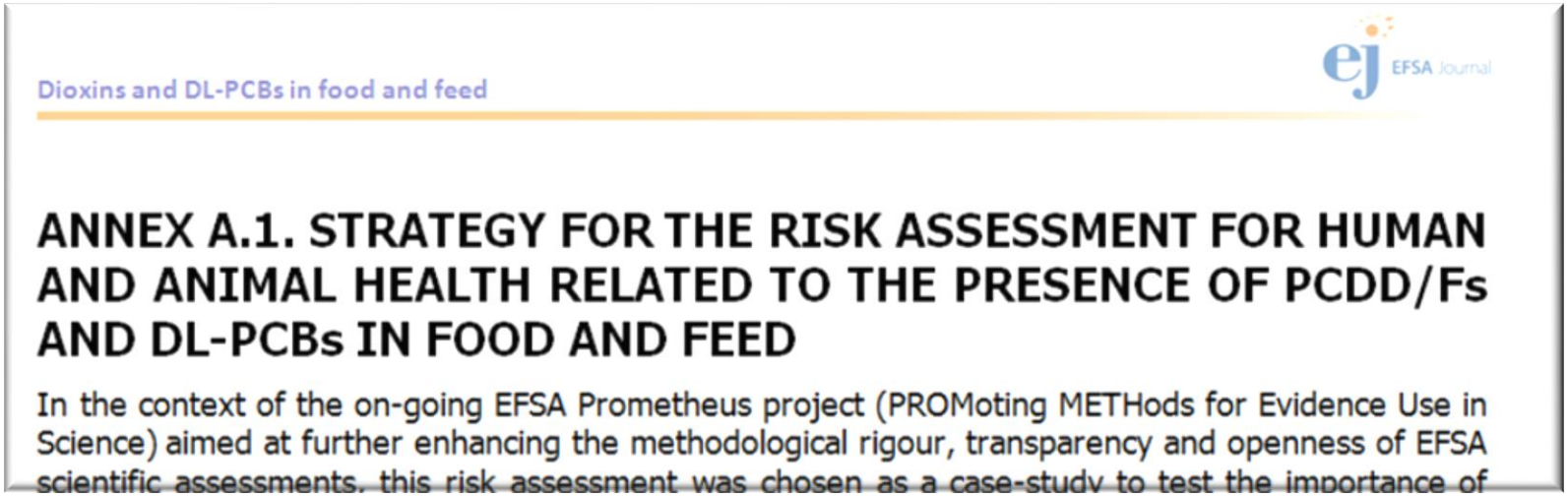
The strategy: the process

- Development of the Risk Assessment strategy

Including:
- piloting of the Extensive literature searches
- development of inclusion/exclusion criteria
- piloting of the critical appraisal tools
- piloting of data extraction

June-December 2015

- Can be found in **ANNEX A** of the opinion



Dioxins and DL-PCBs in food and feed

EFSA Journal

ANNEX A.1. STRATEGY FOR THE RISK ASSESSMENT FOR HUMAN AND ANIMAL HEALTH RELATED TO THE PRESENCE OF PCDD/Fs AND DL-PCBs IN FOOD AND FEED

In the context of the on-going EFSA Prometheus project (PROMoting METHods for Evidence Use in Science) aimed at further enhancing the methodological rigour, transparency and openness of EFSA scientific assessments, this risk assessment was chosen as a case-study to test the importance of