BUNDESINSTITUT FÜR RISIKOBEWERTUNG

BfR

Risiken erkennen – Gesundheit schützen

Proposal for an assessment concept for pesticides with adverse effects on the human endocrine system

Bewertungskonzept für endokrin schädliche Wirkungen auf den Menschen in der Zulassung von Pflanzenschutzmitteln

Karen I. Hirsch-Ernst

New EU pesticide law: Regulation (EC) 1107/2009

concerning the placing of plant protection products on the market

- **Hazard-based "Cut-off" criteria** for the approval of active substances

Annex II, 3.6. Impact on human health

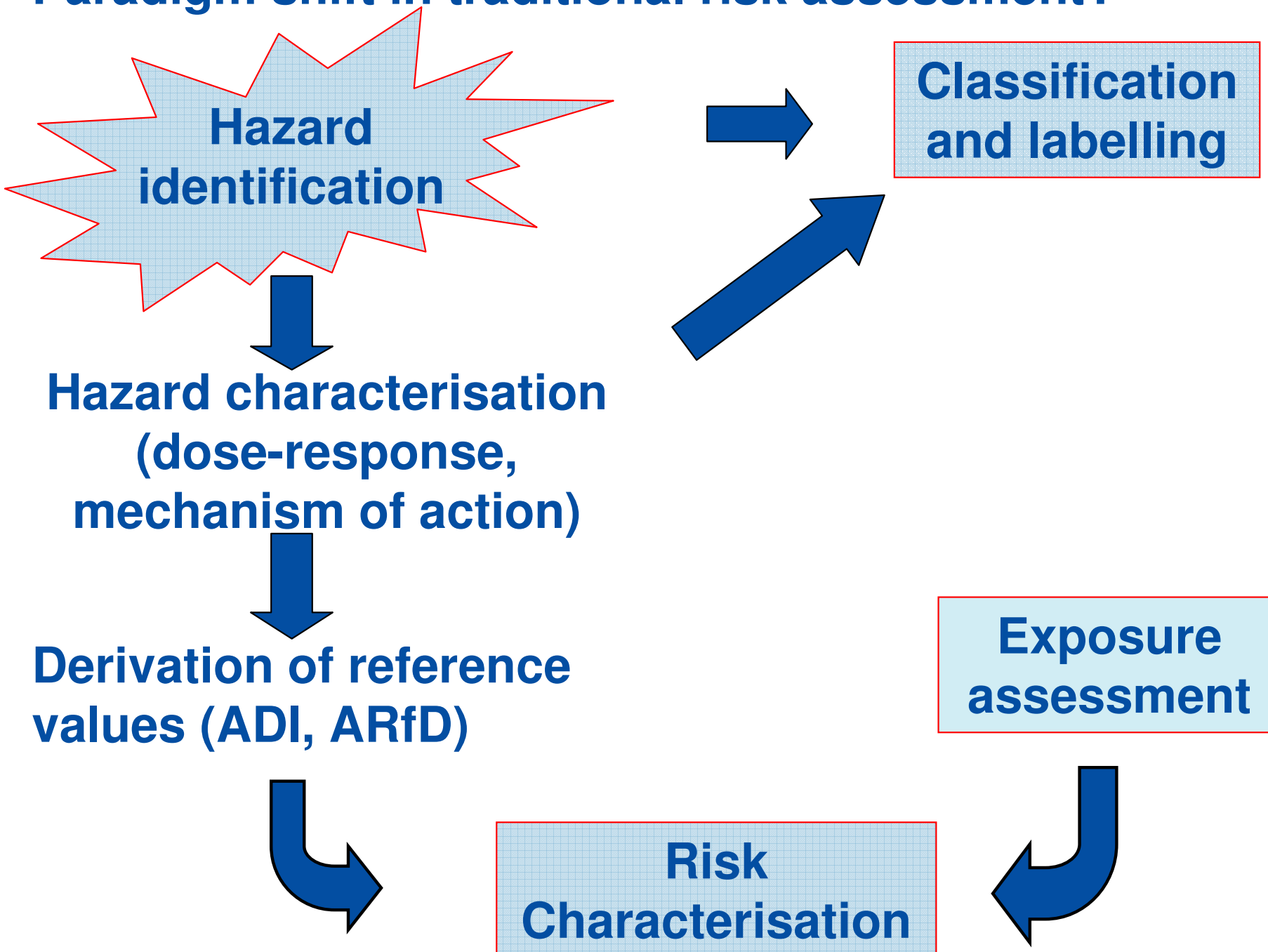
- *An active substance, safener or synergist shall only be approved if …*

… it is not or has not to be classified as …

- *mutagen category 1A or 1B*
- *carcinogen category 1A or 1B*
- *toxic for reproduction category 1A or 1B*

- *… it is not considered to have **endocrine disrupting properties that may cause adverse effects in humans**, unless exposure … is negligible.*

Paradigm shift in traditional risk assessment?



New EU Pesticide Regulation (EC) 1107/2009:
Interim criteria for endocrine disruptors

- **Annex II, 3.6.5.:**

  By 14 December 2013, the Commission shall present … a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted ...

- *Pending the adoption of these criteria …*
  - *substances that are or have to be classified as **carcinogenic category 2 and toxic for reproduction category 2** (Regulation (EC) 1272/2008) shall be considered to have endocrine disrupting properties.*
  - *substances that are or have to be classified as **toxic for reproduction category 2** (Regulation (EC) 1272/2008) and having **toxic effects on endocrine organs** may be considered to have endocrine disrupting properties.*

New pesticide Regulation (EC) 1107/2009

Open issues:

- Definition of Endocrine Disruptor (ED)
- Definition of Adversity
- Development of assessment and decision criteria for substances with endocrine disrupting properties

BfR International Workshop (Berlin, November 2009):

Definition of **Endocrine Disruptor (ED)**

- *An ED is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.*
  (WHO/IPCS 2002)

Definition of **Adversity**

- *A change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences.*
  (WHO/IPCS 2004)

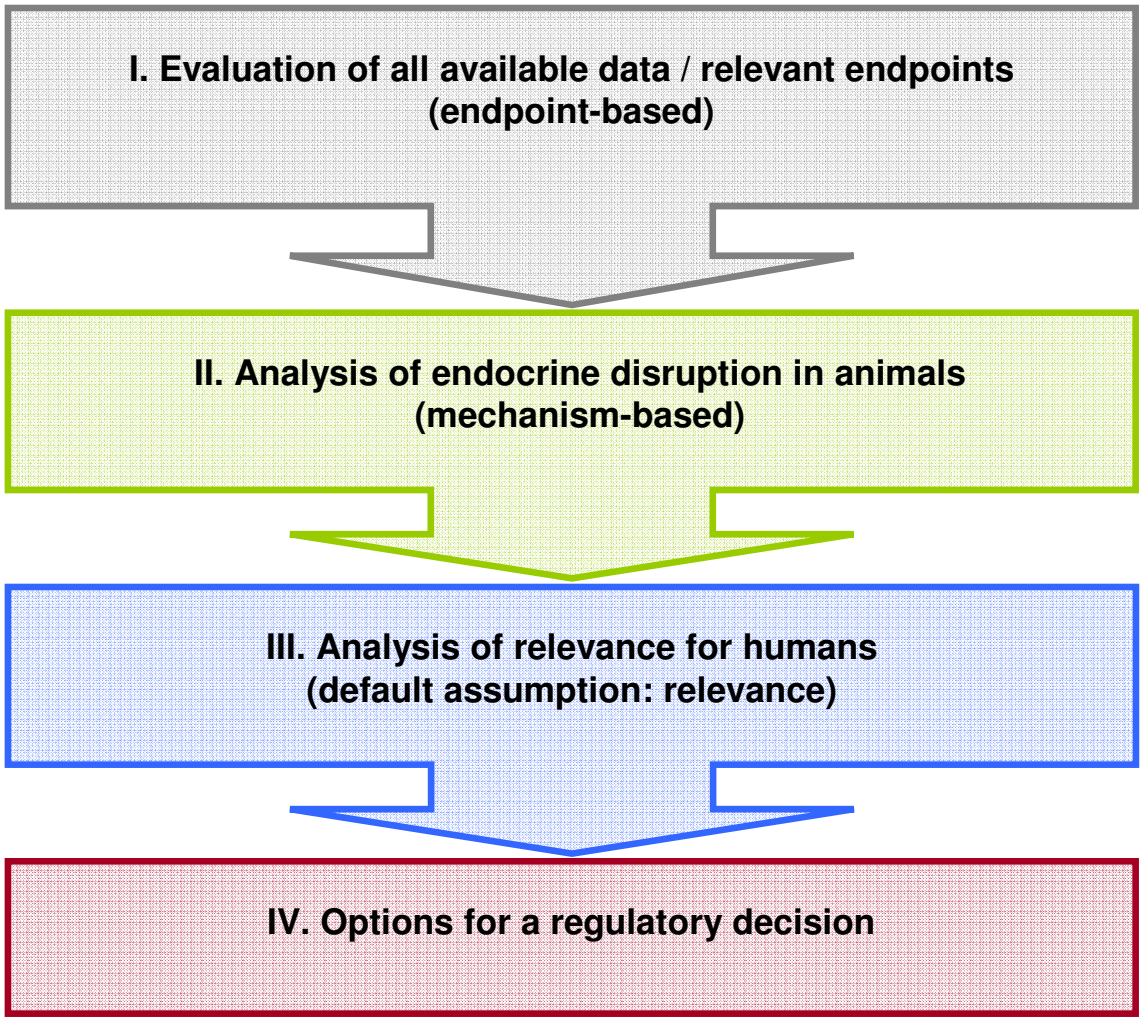
- BfR Workshop Report: see *http://www.bfr.bund.de/*

BfR proposal: Stepwise approach for assessment of endocrine disruptors

Focus on:

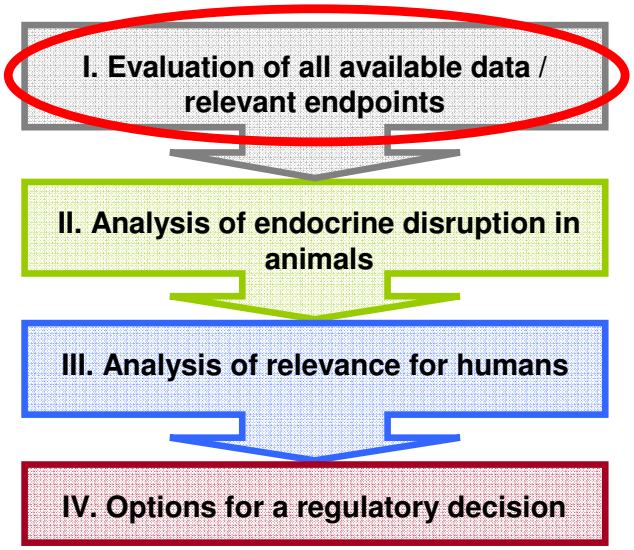
- Active substances in plant protection products
- Regulatory human health risk assessment (not ecotoxicology)
- Assessment and decision criteria

BfR proposal: Stepwise approach for assessment of EDs



Step IV. Option 1: Exposure-based approach
Option 2: Classification-based approach

Step I: Evaluation of data

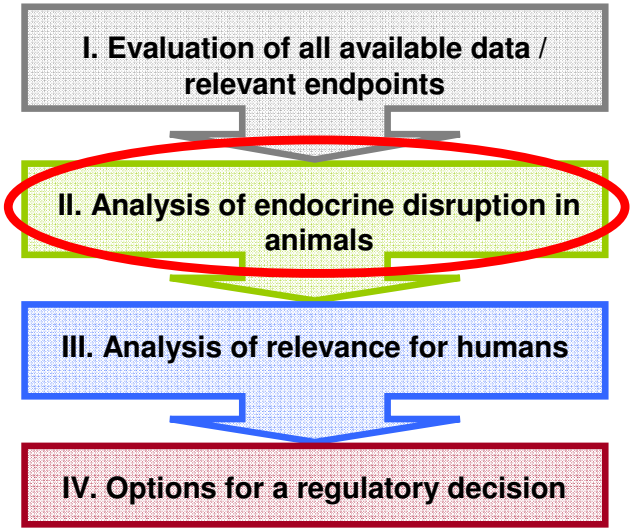


- Consider **all available data** and **relevant endpoints,** especially the following regularly required **mammalian toxicology studies**:
  - Short-term toxicity studies;
  - Long-term toxicity and carcinogenicity studies;
  - Multigeneration reproductive toxicity studies;
  - Developmental toxicity studies.

- These studies represent the current **highest tier tests** for detecting ED properties in mammals.

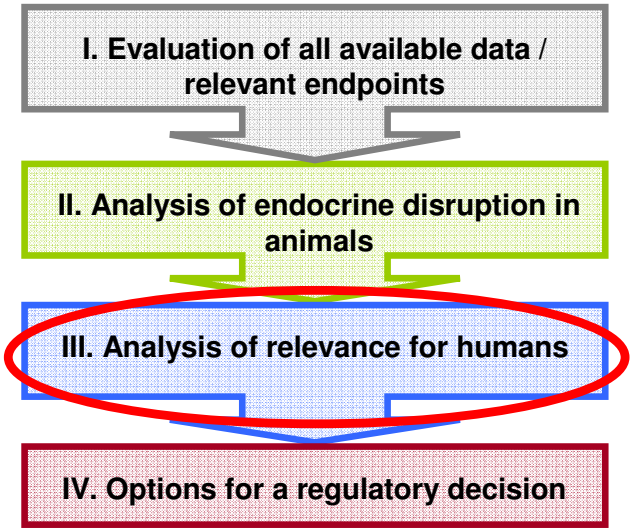
- Additional **mechanistic data** may be required to support a certain mechanism/mode of action (MOA).

Step II: Analysis of ED in animals



- Consider **all relevant endocrine mechanisms** and **systems,** e. g.:
  - Hypothalamic-pituitary-gonadal axis;
  - Hypothalamic-pituitary-thyroid axis;
  - Adrenal and pancreatic systems;
  - Systems involved in energy metabolism;
  - Calcium homeostasis etc.
  - …

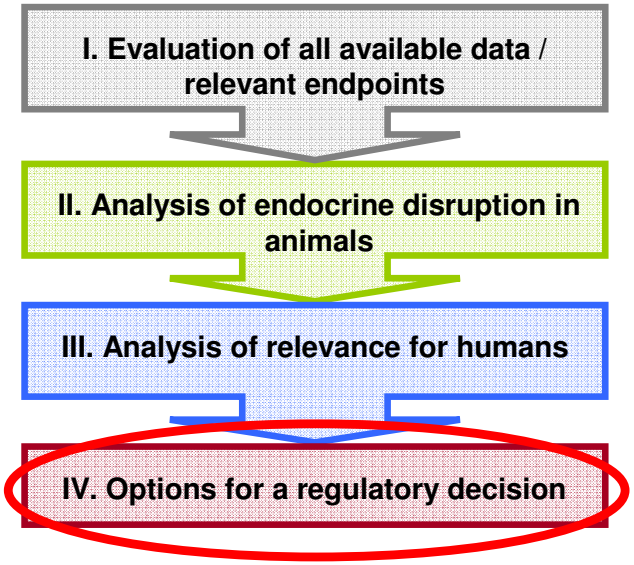
Step III: Analysis of relevance for humans



- Analysis of **relevance to humans** by use of a **structured framework**, e. g.:
  - IPCS framework for analyzing the relevance of a **cancer mode of action** for humans (Boobis et al., 2006);
  - IPCS framework for analyzing the relevance of a **noncancer mode of action** for humans (Boobis et al., 2008);
  - Other feasible human relevance frameworks may be considered.

- **Default assumption is that effects are relevant to humans.**

Step IV – Option 1: Exposure-based approach



- Consider all **intended uses** and all **exposure scenarios,**
  taking into account specific groups of the population:
  - Consumers;
  - Operators;
  - Bystanders;
  - Residents.

- **No approval**: exposure of humans is higher than negligible.
- **Approval**: exposure of humans is negligible.

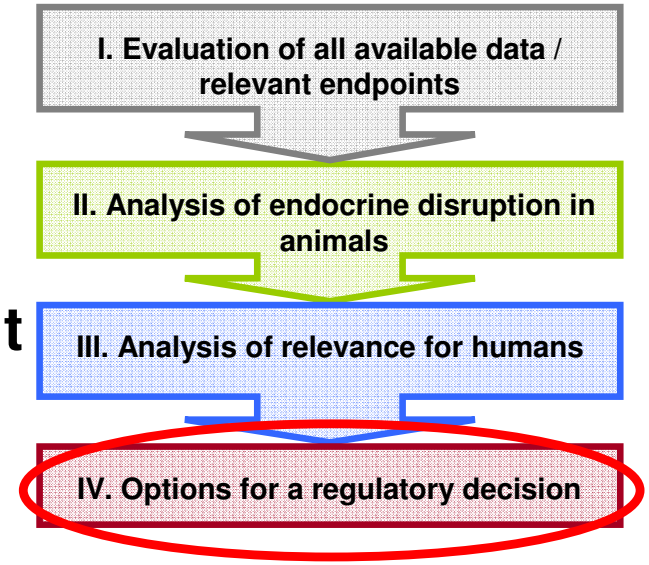
Definition of "negligible exposure" by Regulation (EC) 1107/2009:

- **Maximum residue level (MRL) at 0.01 mg/kg** (*Comment: A common MRL for all substances is not a scientific decision criterion to protect consumers*).
- **Closed systems** (*Comment: Closed systems do not necessarily exclude exposure of bystanders and residents*).

Recommendation:

A science-based definition of negligible exposure is required. Such a definition might for example be based on 10% of the ADI or on the TTC concept.

Step IV – Option 2: Classification-based approach



- **Proposal for a classification-based decision about approval of active substances:**
  - **No approval**: Classification as ED category 1.
  - **Approval**: Classification as ED category 2.
    - Substances go into regular risk assessment, also in cases of combinations of classifications (e.g. with C2 and/or R2).
  - **Approval**: Evidence for ED, but criteria for classification not fulfilled.

Step IV – Option 2: Classification-based approach

Proposed classification for ED

(Criteria are based on Regulation (EC) No. 1272/2008, and adjusted for ED effects)

Category 1: Substances are classified in Category 1 for endocrine disruption (ED) on the basis of:

- reliable and good quality evidence from **human** cases or epidemiological studies.
- observations from appropriate studies in experimental **animals** in which **severe** toxic effects on the endocrine system, assumed to be of relevance to human health, were produced at generally **low** exposure concentrations (i.e. 5-30 mg/kg bw/day).

Category 2: Substances are classified in Category 2 for (ED) on the basis of:

- observations from appropriate studies in experimental **animals** in which significant toxic effects on the endocrine system, assumed to be of relevance to human health, were produced at generally moderate exposure concentrations (i.e. 50-300 mg/kg bw/day).

Step IV – Option 2: Classification-based approach

Proposed classification criteria for ED:

- Criteria are essentially based on Regulation (EC) No. 1272/2008, section 3.9. ***Specific Target Organ Toxicity – Repeated Exposure (STOT-RE)*** and adjusted for the specific endpoints which may be adversely affected by EDs.

Proposed guidance values (mg/kg bw/day) for ED category 1 or category 2:

Study type	ED category 1	ED category 2
28-day oral toxicity	≤ 30	≤ 300
90-day oral toxicity	≤ 10	≤ 100
Chronic toxicity	≤ 5	≤ 50

- The guidance values are intended to be used as part of the weight of evidence approach, and to assist with decisions about classification.
- The guidance values are not intended as strict demarcation values.

BfR proposal – Summary

- BfR proposal includes specific scientific criteria for assessment of ED effects on **human health**

- **Stepwise approach**, with 2 Options for the regulatory decision (step IV):
  - Option 1: **Exposure-**based approach
  - Option 2: **Classification-**based approach

- The proposed specific scientific assessment criteria are principally suitable for:
  - Pesticides
  - Biocides
  - Chemicals (limited database may require adjustment of criteria)

Next actions intended

- Publication of major workshop results in a scientific journal

  The report on the BfR Workshop (Berlin, November 2009) is available via the BfR website at:

  http://www.bfr.bund.de/cd/240

- Testing of proposed specific criteria for EDs in plant protection products on a set of active substances

- Publication via the BfR website of a draft concept paper on development of a stepwise procedure for the assessment of substances with endocrine disrupting properties according to the plant protection products regulation

- Discussion on further measures with European Commission, EFSA and member state authorities (AFSSA,….)

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Thank you for your attention

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