Webinar | 9 October 2025

EFSA'S OPINION ON THE USE AND REPORTING OF HISTORICAL CONTROL DATA (HCD) FOR REGULATORY STUDIES

STARTING AT 15:00

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TODAY'S SPEAKERS & CONTRIBUTOR

Arianna Chiusolo
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Basel University
Chair of the HCD Working Group

Laura Martino
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MESE Unit, EFSA

Anna Lanzoni
Senior Scientific Officer
PREV Unit, EFSA

AGENDA

Starting time 15:00

Background and mandate
Arianna Chiusolo

Mandate interpretation, process, methodology & decision scheme
Martin Wilks

Case study on dichotomous data
Laura Martino

Scientific Opinion and Annexes
Arianna Chiusolo

Follow up activities and final remarks
Arianna Chiusolo

Ending time 16:00

BACKGROUND (1)

- The submission of HCD is a legal requirement[1] in the context of the peer review of the pesticide risk assessment of an active substance:
  - *"Where available, historical control data shall be provided routinely. The data submitted shall be for **endpoints that could represent critical adverse effects**, and shall be **strain-specific** and from the **laboratory** which carried out the index study. They shall cover a **five-year period**, centred as closely as possible on the date of the index study".*
  - Subchapters 5.5 and 5.6:*"Where submitted, HCD shall be from the same species and strain, maintained under similar conditions in the same laboratory and shall be from contemporaneous studies. Additional HCD from other laboratories may be reported separately as supplementary information".*

[1]Commission Regulation (EU) No 283/2013 setting out data requirements for active substances, in accordance to Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

BACKGROUND (2)

- Currently, the HCD are mainly used for the interpretation of experimental results and evaluation of critical adverse effects e.g. in carcinogenicity and in reproductive/developmental toxicity studies.
- The compilation, reporting and use of HCD for the assessment of toxicity studies is not harmonised across applicants and Member State competent authorities leading to inconsistency in the peer review process.
- Recommendations needed for collation, reporting and use of HCD.
- Although this is an urgent need for the pesticide peer review process, the use of HCD for the interpretation of toxicity studies is of general interest.

MANDATE

The Plant Protection Products and its Residues (PPR) Panel self-tasked to develop a Scientific Opinion with the aim to:

1) Elucidate the requirements for the use of HCD for interpretation of studies used for regulatory purposes, including carcinogenesis and repro-developmental toxicity studies
2) Clarify how HCD should be compiled as part of the regulatory dossier
3) Assist on the interpretation of HCD in the context of evaluation of regulatory studies

Deadline: 30 Jun 2025

WORKING GROUP COMPOSITION

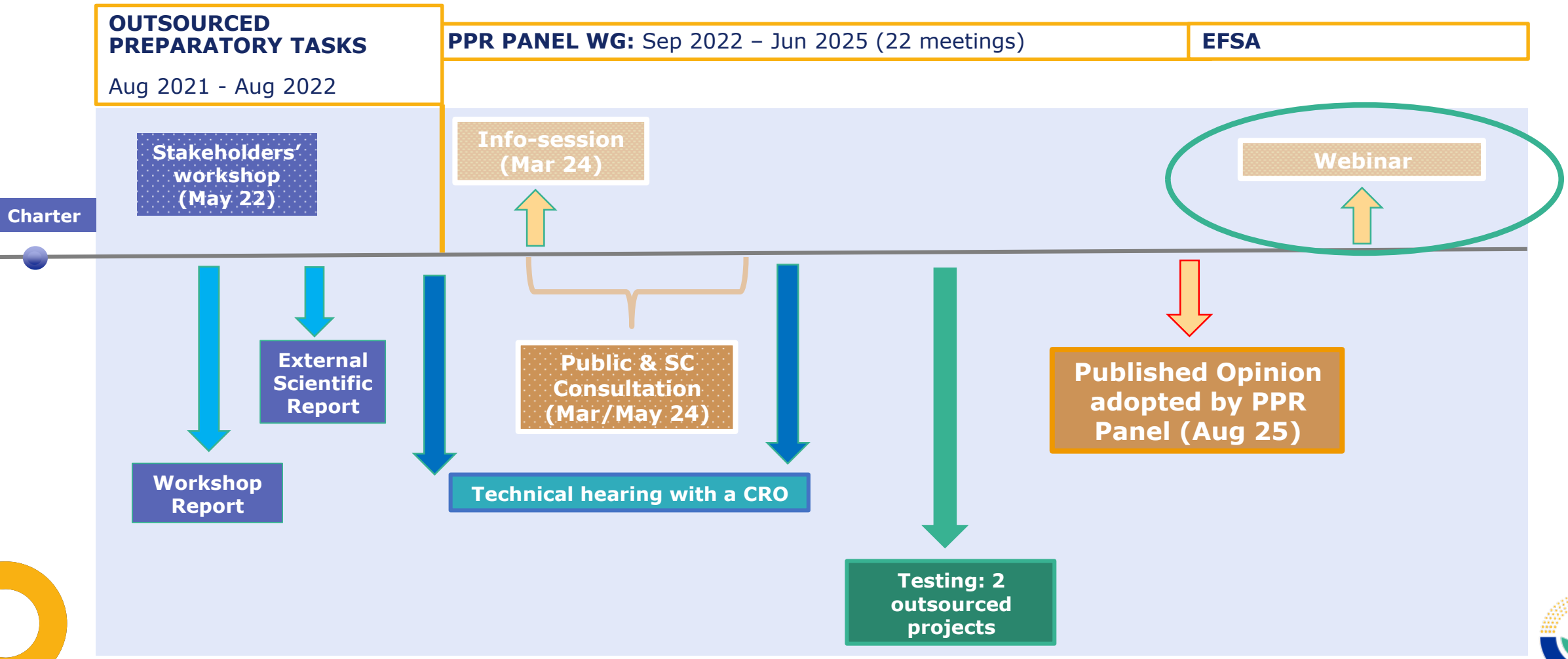
- Chair: Martin Wilks (PPR Panel)
- Members: Tamara Coja (PPR Panel), Ian Dewhurst, Peter Craig, Emily McVey (PPR Panel), Bertrand Desprez
- PREV Unit: Arianna Chiusolo, Anna Lanzoni, (Andrea Terron & Tommaso Giorgi)
- MESE Unit: Laura Martino, Sara Levorato

MANDATE TORS INTERPRETATION

1) Elucidate the requirements for the use of HCD for interpretation of studies used for regulatory purposes, including carcinogenesis and repro-developmental toxicity studies
   - Criteria for the adequacy of the historical control dataset, which includes comparability of studies and the quality, and methods for analysis
2) Clarify how HCD should be compiled as part of the regulatory dossier
   - Requirements on how to compile and report HCD
3) Assist on the interpretation of HCD in the context of evaluation of regulatory studies
   - Recommendations on the use of HCD in the evaluation of the regulatory study (index study)

Deadline: 30 Jun 2025

PROCESS


OUTSOURCED PREPARATORY TASKS
Aug 2021 - Aug 2022
PPR PANEL WG: Sep 2022 – Jun 2025 (22 meetings)
EFSA
Stakeholders' workshop (May 22)
Info-session (Mar 24)
Webinar
Charter
External Scientific Report
Public & SC Consultation (Mar/May 24)
Published Opinion adopted by PPR Panel (Aug 25)
Workshop Report
Technical hearing with a CRO
Testing: 2 outsourced projects

METHODOLOGY

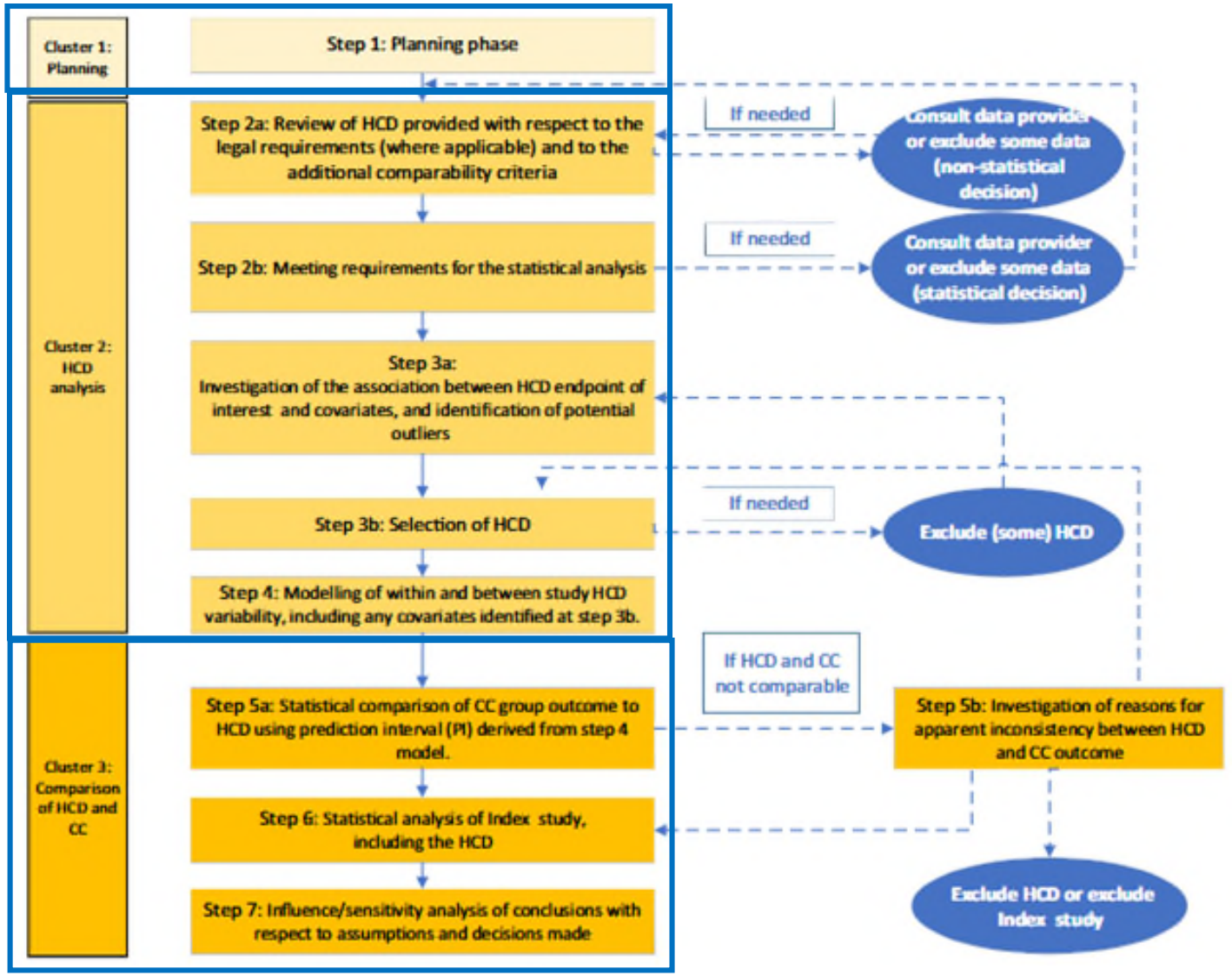
- Compilation of examples from pesticides and biocides area
- Development of methodological approach for the use of HCD, considering available relevant literature and Scientific Committee & Public Consultation
  - Decision scheme to guide step-by-step in the evaluation of HCD acceptability and integration in the assessment of the index study
  - Illustrative case studies
  - Real-data case studies (2 outsourced projects to BfR)
  - Templates for reporting HCD for different endpoints (mamtox & ecotox)

* Grant Deliverables:
- Workshop Report at https://zenodo.org/records/6956943#.YxlWuXZByUk
- External Scientific Report at https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2022.EN-7558

DECISION SCHEME

Need for a trained statistician

Time for the analysis



A priori plan - not data driven

Structured and reproducible approach

Enhanced power

Dialogue statisticians/domain experts

CASE STUDY - DICHOTOMOUS ENDPOINT

Index study characteristics:

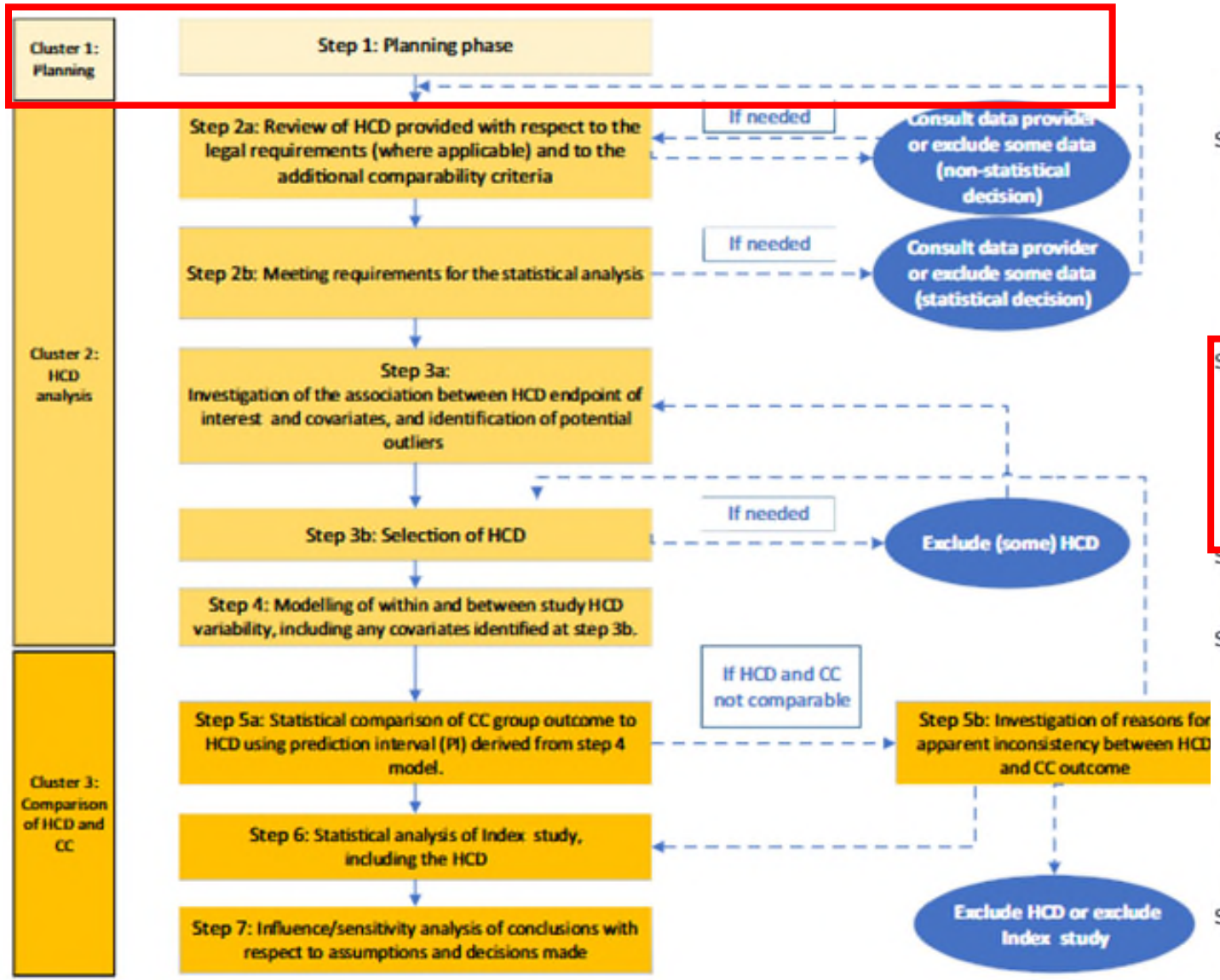
- Endpoint: pathological finding (presence/absence)
- 5 arms (1 control, 4 doses: 10, 50, 1500, 10000 ppm test item)
- Type of study: combined onc./tox
- Route of exposure: diet
- Diet: laboratory animal diet
- Year: 1991
- Species: rat (5 per cage)
- Gender: male
- Strain: Sprague-Dawley
- Study period: 104 weeks
- Lab: Painting lab

Historical Control Data

- N studies: 23
- Type of studies: oncogenicity, combined onco/tox, dietary comparison
- Route of exposure: diet, oral gavage, subcutaneous
- Diet: laboratory animal diet; rodent maintenance diet.
- Years: 1988-1994
- Species: rat (1 or 5 per cage depending on the study)
- Gender: male
- Strain: Sprague-Dawley
- Study period: varying from 89 to 104 weeks
- Lab: Painting lab

This is a fictional example although inspired by a true one

STEP 1: PLANNING



Step 2a: Assess the HCD with respect to legal requirements and additional comparability criteria (Annex D), subject to limitations due to the use of artificial data. Consider whether exclude group(s) of studies for which the value of the covariate differs from the index study. If some data are excluded, Step 3a will be revisited for the reduced dataset.

Step 4: Fit a statistical model of between- and within-study variability to HCD, possibly incorporating effects of covariates.

Technical details: A beta-binomial model (see Section A.2.3 of Appendix A of the Opinion) will be used, as the endpoint represents a rare finding making it desirable to use tests with exact p-values at step 6 (see Sections A.2.3 and A.3.6.3 of Appendix A of the Opinion). Maximum likelihood estimation will be applied and profile likelihood used for confidence limits on effective sample size (see Section A.3.4.3 of Appendix A of the Opinion).

Step 5a: Apply Approach 2 to Step 5a, because the endpoint is for a rare finding.

Technical details: A prediction interval (PI) will be computed for the outcome (number of animals with the finding) in another control group, based on the number of animals examined in the concurrent control (CC) (see Section A.3.5.3 of Appendix A of the Opinion). The intended probability level for the PI is 95% but this may be exceeded due to the discreteness of the predictive distribution. The 95% upper confidence limit from Step 4 for the effective sample size parameter will be used when computing the PI.

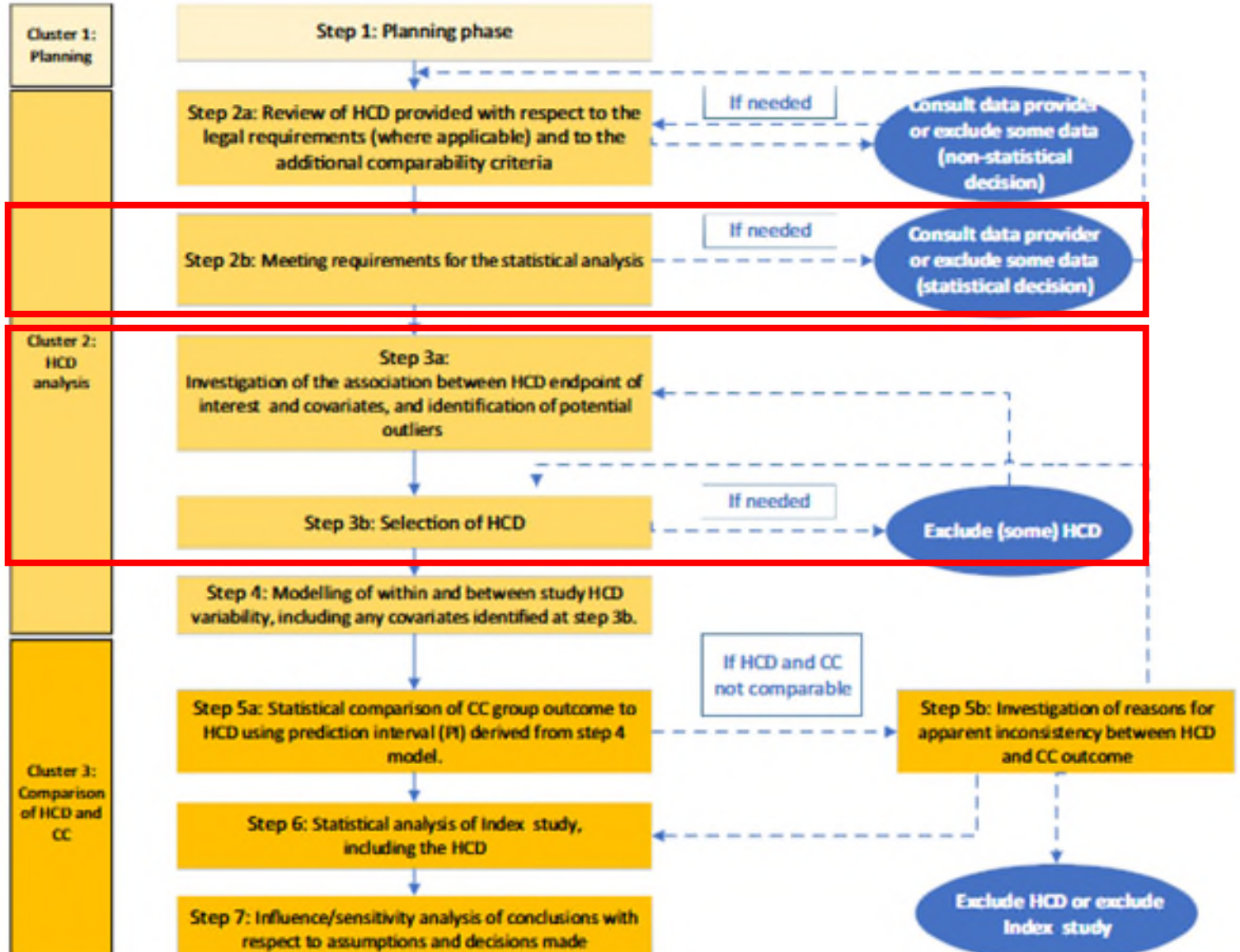
Step 5b: Verify whether the number of animals with the finding in the CC lies in the PI from Step 5a. If so, proceed to Step 6. Otherwise, consider what action to take following the suggestions in Step 5b of the decision scheme in the Opinion.

Step 6 [conditional on the outcome of Step 5b]: Analyse the index study, including information from HCD. Index study data and information from HCD will be summarised graphically. The Tarone test (Tarone, 1982) for a dose-response trend will be applied, as a generalization of the Cochran–Armitage test to incorporate information from HCD (see Section A.3.6.3 of Appendix A of the Opinion).

Technical details: Confidence intervals for the graphical summary will follow the method of Wilson (1927), as recommended by Agresti and Coull (1998) and Brown et al. (2001). These will be shown for index study groups, for pseudo-data contributed to the Tarone test by HCD, and for CC pooled with pseudo-data from HCD. The exact p-value for the Tarone test will be calculated based on Hoel and Yanagawa (1986).

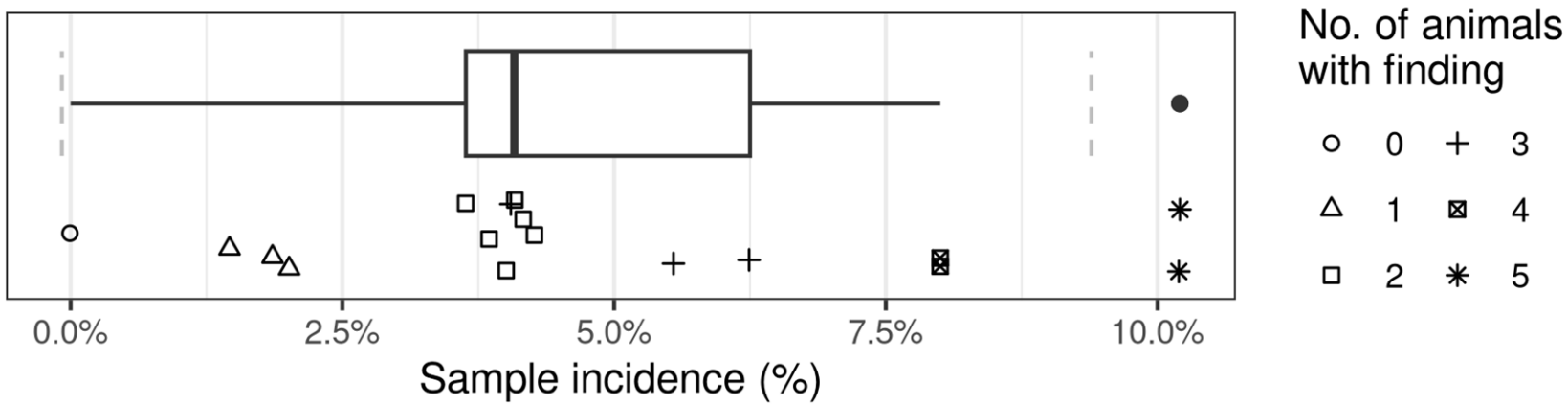
Step 7: Investigate how the outcome would be affected by different assumptions at earlier steps, for example to include data that were excluded in Step 3b or applying comparability criteria more strictly in Step 2a.

STEP 2 & 3


Cluster 1: Planning
Step 1: Planning phase
Step 2a: Review of HCD provided with respect to the legal requirements (where applicable) and to the additional comparability criteria
If needed
Consult data provider or exclude some data (non-statistical decision)
Step 2b: Meeting requirements for the statistical analysis
If needed
Consult data provider or exclude some data (statistical decision)
Cluster 2: HCD analysis
Step 3a: Investigation of the association between HCD endpoint of interest and covariates, and identification of potential outliers
Step 3b: Selection of HCD
If needed
Exclude (some) HCD
Step 4: Modelling of within and between study HCD variability, including any covariates identified at step 3b.
Cluster 3: Comparison of HCD and CC
If HCD and CC not comparable
Step 5a: Statistical comparison of CC group outcome to HCD using prediction interval (PI) derived from step 4 model.
Step 5b: Investigation of reasons for apparent inconsistency between HCD and CC outcome
Step 6: Statistical analysis of Index study, including the HCD
Exclude HCD or exclude Index study
Step 7: Influence/sensitivity analysis of conclusions with respect to assumptions and decisions made

STEP 3.A IDENTIFICATION OF POTENTIAL OUTLIERS

Dot-plot and box-and-whisker plot of sample incidence of finding in HC studies



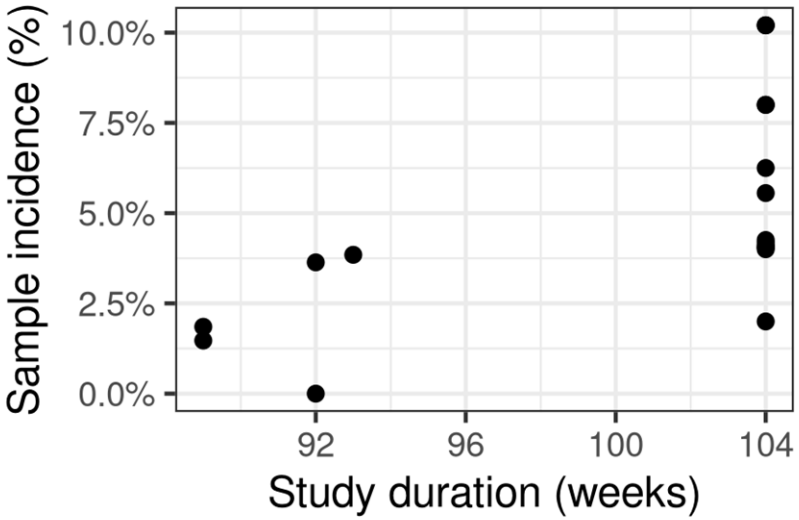
Points in dot-plot randomly jittered vertically to distinguish multiple studies having similar incidence. Clusters corresponding to the number of animals having the finding: 0, 1, 2, 3, 4 and 5. Such clustering is inevitable for dichotomous endpoints. Vertical grey dashed lines indicate conventional "fences" for outlier detection in a box-and-whisker plot of continuous data.

Although two studies with incidence greater than 10% lie just beyond the upper fence, the inevitable clustering of dichotomous data means that they are not unexpected.
Residuals were assessed for a generalised linear model fitted to the data. Shapiro-Wilks test did not indicate any departure from normality -> **Conclusion: no obvious potential outliers**.

Reasons for being an outliers should be investigated. Exclusion of outliers should not be the default option. Interaction statistician/domain experts is key!!!

STEP 3.A INVESTIGATION OF ASSOCIATION BETWEEN ENDPOINT AND COVARIATES

Graphical exploration of association



Statistical testing for association

Covariate	P-value
Route of exposure (diet or subcutaneous)	0.84
Study type (oncogenicity or combined oncogenicity/toxicity)	0.89
Diet (laboratory animal diet 1 or 2 or rodent maintenance diet)	0.76
Animals per cage (number)	0.90
Study start date	0.45
Study duration (weeks)	**0.008**

Statistically significant association found **between study duration and incidence**. No statistically significant association for other covariates.

Caveats in the use of tests: Lack of significance should not be interpreted as absence of differences between levels (frequently power is low due to the limited numbers of categories and limited sample size for some categories).

Need to interpret results with caution

STEP 3.B SELECTION OF HCD

Conclusions from step 3.a

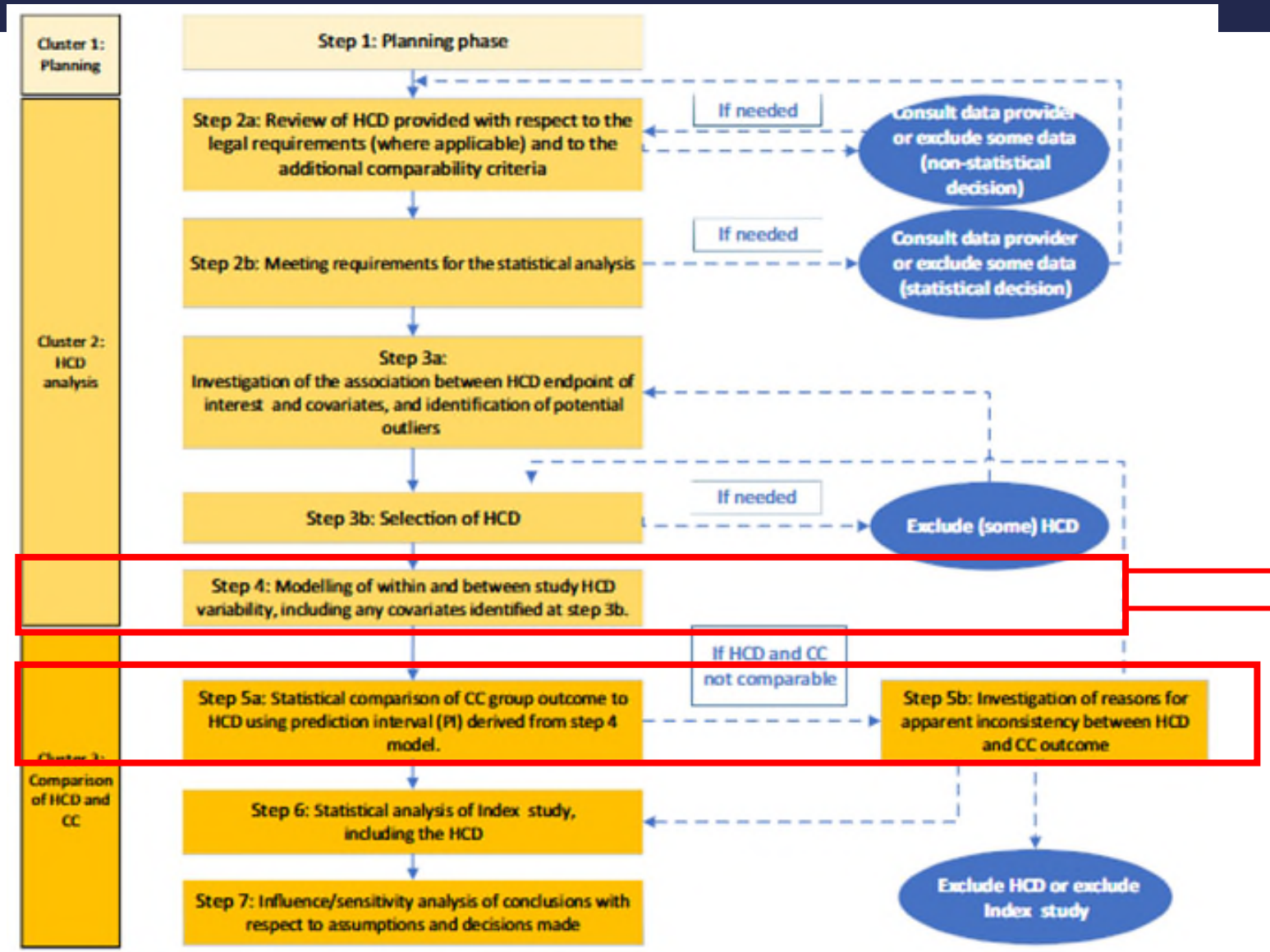
Evidence of association between endpoint and study duration.

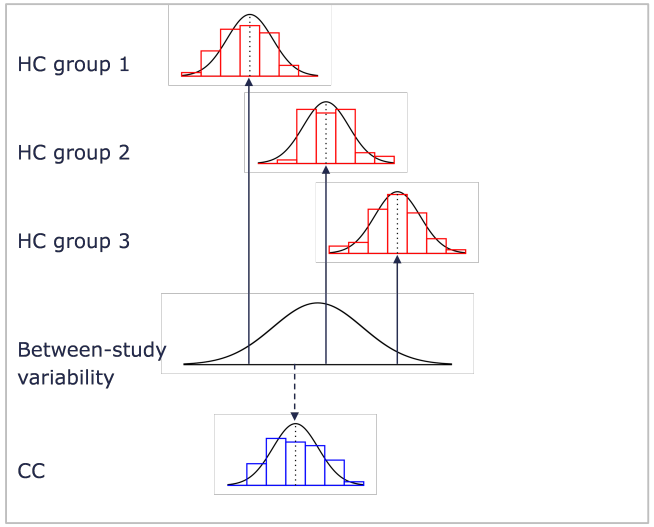
Decision: exclude the 7 HC studies with duration less than 104 weeks because of the association, in line with biological expectation that the pathological finding often develops late in an animal's life and consequent potential for significant bias with respect to incidence of the finding for the HC studies with duration 94 weeks or less.

Differences in route of exposure, diet and study type were not considered biologically important in relation to occurrence of the pathological finding.
The final HCD consisted of results for 16 HC groups.

Interaction statistician/domain experts is key!!!

STEP 4 & 5



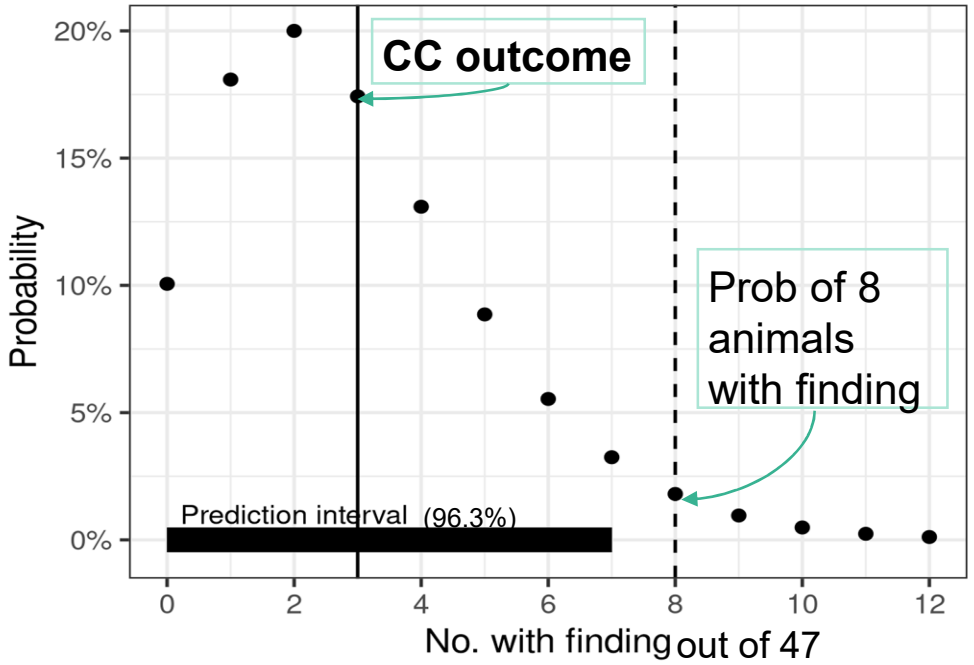


Use models that account for within and between study variability -> Beta-binomial model with beta distribution for between-study variability of incidence and binomial distribution for the outcome (number of animals with finding) of a single control group

STEP 5.A STATISTICAL COMPARISON OF CC AND HCD

Approach 2 (CC assumed similar to HCD unless shown different):

Outcome of a further control group (based on HCD):

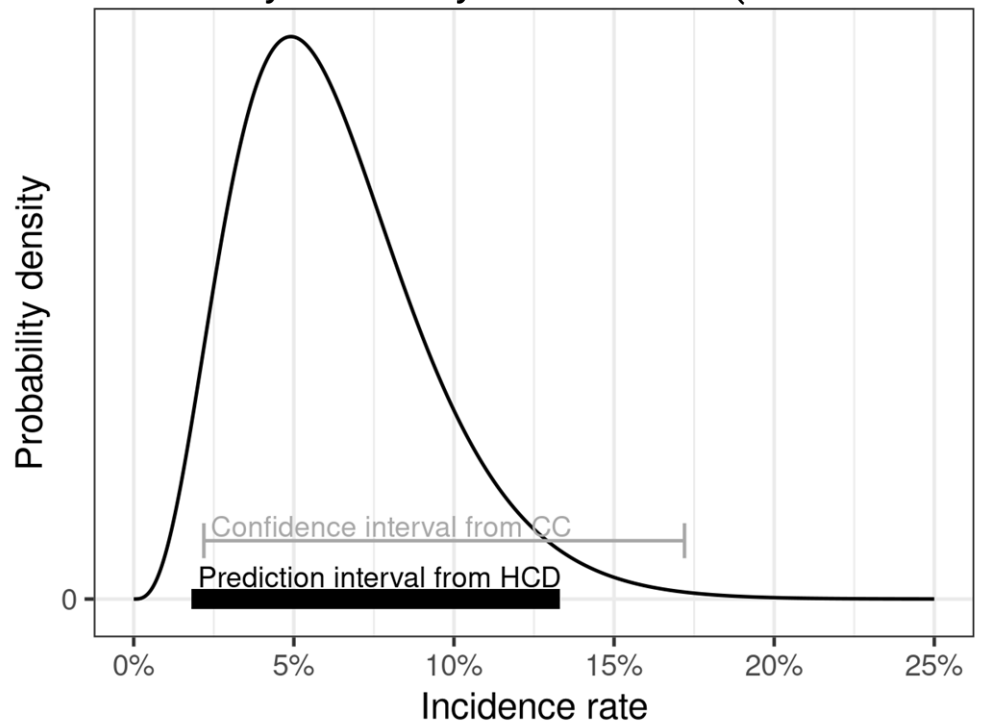


CC lies in PI from HCD ⇨ **Step 6**

Alt. scenario: CC not in PI ⇨ Step 5b

Approach 1 (CC incidence assumed different from HCD unless shown similar):

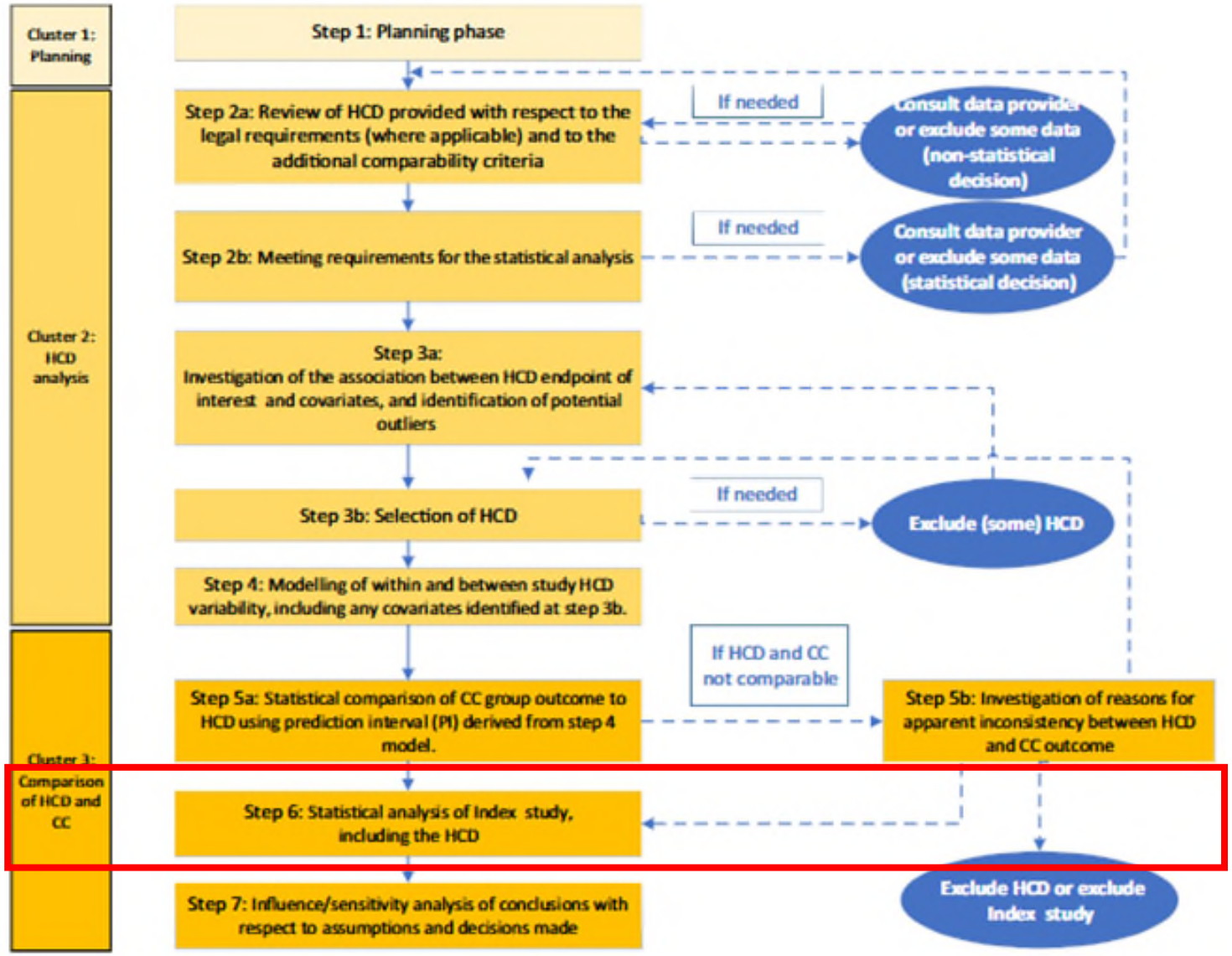
Between-study variability of incidence (based on HCD):



CI from CC not inside PI from HCD

⇨ **Step 5b**

STEP 6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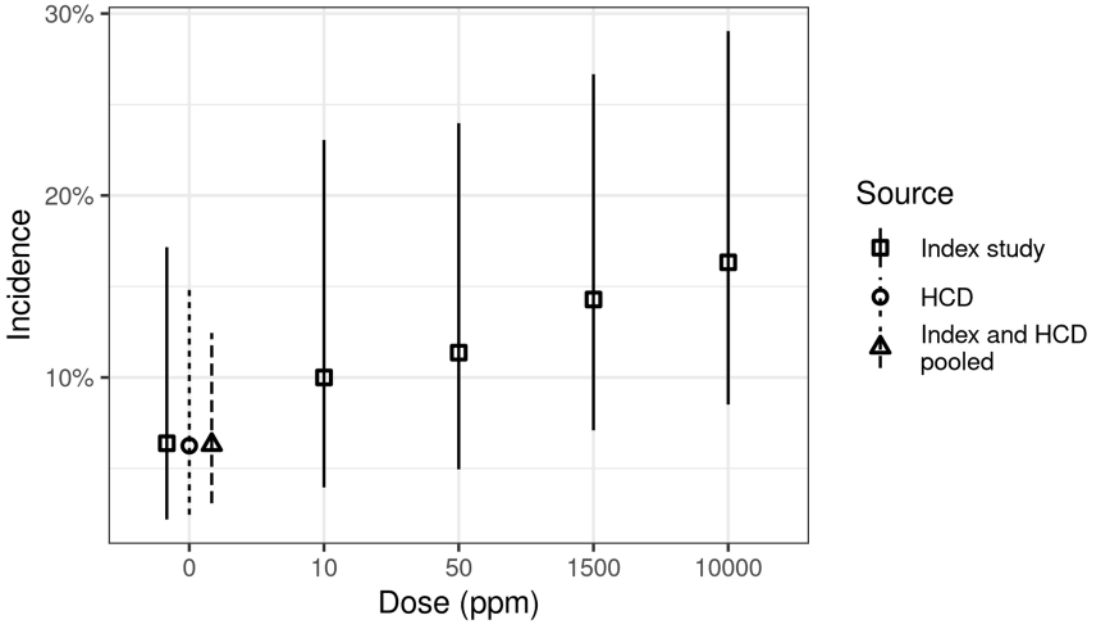
STEP 6. STATISTICAL ANALYSIS OF CURRENT STUDY, INCLUDING THE HCD

Index study (with information from HCD)



Statistical tests for dose-related trend

Test	Data	P-value
Cochran-Armitage	Index study (without HCD)	0.104
Tarone	Index study + information from HCD	**0.036**

Statistical tests comparing highest dose to control

Test	Data	P-value
Fisher exact test	Index study (without HCD)	0.113
Tarone	Index study + information from HCD	**0.031**

Influence of HCD

- Trend test (Cochran-Armitage) did not find significant evidence of trend using conventional 0.05 threshold. **HCD change conclusion increasing the evidence of trend (lower P-value).**
- HCD did change conclusion for comparison of highest dose to control: **statistically significant difference when HCD included**.
- Weight given to HCD is determined by the between-study variability: in this example **HCD contribute pseudo data equivalent of 64 additional control animals of which 4 had the pathological finding**.

DRAFT SCIENTIFIC OPINION AND ANNEXES

ANNEX
Case stu
ANNEX
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ANNEX E

Template for presenting HCD for histopathology in repeated dose toxicity studies

ANNEX F

Template for presenting HCD for endpoints in reproductive toxicity studies

ANNEX G

Template for presenting HCD for endpoints in developmental toxicity studies

ANNEX H

Template for presenting HCD for endpoints in bird reproduction studies

ANNEX I

Template for presenting HCD for endpoints in fish chronic studies

ANNEX J

Template for presenting HCD for endpoints in amphibian developmental studies

FOLLOW UP ACTIVITIES

- Communication and stakeholder engagement
  - Today webinar to present the methodology and gather feedback.
  - Two physical trainings for Member States in Q1–Q2 2026:
    - 1 toxicologist + 1 statistician per Member State.
    - Focus on methodology and practical case studies.
  - Surveys and interviews with Member States to identify further implementation needs.
- Further activities under consideration:
  - Engagement with other stakeholders.
  - Development of e-learning materials and statistical tool to support implementation.

STAY TUNED

FINAL REMARKS

- Structured and reproducible methodology.
- Enhances transparency, scientific robustness, and regulatory confidence.
- Requires additional resources (notably statistical expertise), but offers clear methods for planning, evaluation and analysis.
- Improves consistency across assessments through harmonised reporting and templates.
- Emphasizes collaboration between toxicologists and statisticians throughout the process.
- Supports implementation of the 3R principles and enables future harmonisation across sectors beyond pesticides.

Thank you for your attention and engagement—your feedback and collaboration will be key to shaping the next steps in the implementation of this methodology

THANK YOU FOR ATTENDING OUR WEBINAR!

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