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Uncertainty quantification methods for complex models used in drug development and/or regulatory approval

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CONFIRMS Consortium

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CONsortium **F**or **I**nnovation in **R**egulatory Medical **S**tatistics - **CONFIRMS**

- **Pharmacometrics Research Group at Uppsala University (UU)**
  - Andrew Hooker, Mats Karlson, Xiaomei Chen, Yevgen Ryeznic, Zhe Huang
  - Sub-contractor: **Swedish Medical Products Agency (MPA)**, Robin Svensson
- **Center for Medical Data Science** (CEDAS), **Medical University of Vienna (MUW)**
  - Martin Posch, Franz König
- **Department of Medical Statistics, University Medical Center Göttingen (UMG)**
  - Tim Friede, Norbert Benda, Paula Starke, Lucia Schneider
- **Austrian Medicines and Medical Devices Agency** (MEA), a business division of the Austrian Agency for Health and Food Safety **(AGES)**
  - Florian Klinglmueller, Tobias Fellinger, Elham Yousefi, Lynette Caitlin Mikula

Uncertainty in Complex Models: Key Challenges

- **Role of Complex Models**: Physiologically Based Pharmacokinetic (PBPK), quantitative systems pharmacology (QSP), and machine learning (ML) models are essential for drug development tasks like dose prediction, drug-drug interaction assessment, and clinical trial design.
- **Current Limitations**:
  - Parameters often fixed without accounting for uncertainty or variability.
  - Discrepancies assessed using simplistic metrics (e.g., fold prediction error), which lack sensitivity and pharmacological relevance.
- **Gap & Opportunity**:
  - No widely accepted uncertainty quantification (UQ) methods for complex models.
  - Emerging UQ techniques can improve model credibility and support regulatory decision-making.

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Confirms consortia project objectives

1. **Identify UQ Methods (literature review)**: Summarize current statistical methods applicable to complex models (PBPK, QSP, ML) for drug development and regulatory use.
2. **Assess Performance**: Conduct simulations to evaluate selected methods under various settings and derive recommendations.
3. **Promote Application**: Publish results and provide an easy-to-use toolkit with tutorials for implementing UQ in complex modeling.

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Literature Review

Two parts:

1. **Literature Review:** The review identifies UQ methods in PBPK, QSP, ML models and cross-disciplinary techniques from other sciences

2. **Review of regulatory procedures where uncertainty quantification of mechanistic models was of concern:** The review identifies EMA procedures discussing UQ, maps methods, and summarizes regulatory recommendations.

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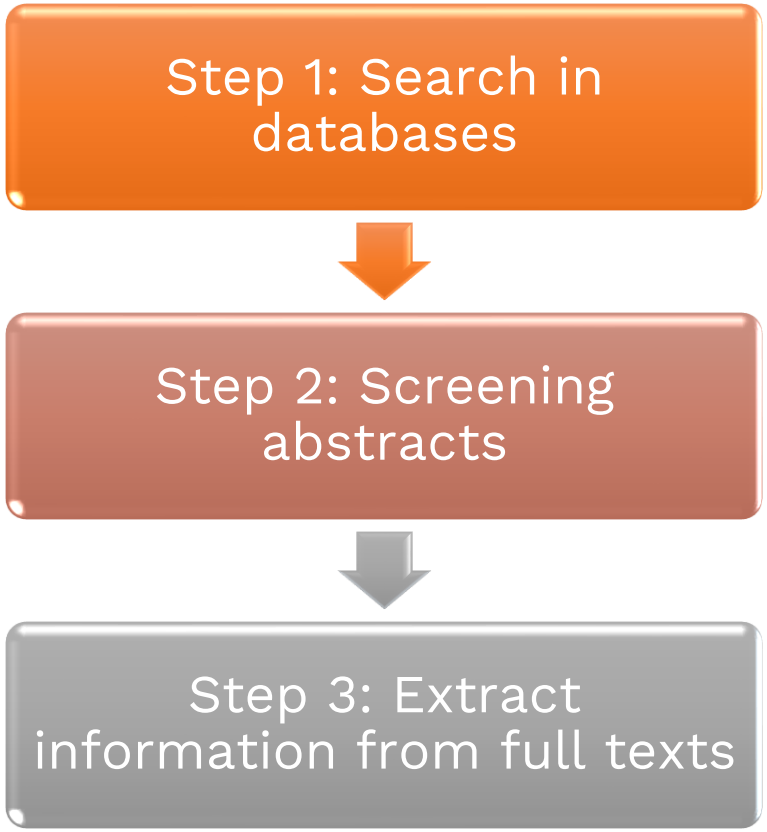
Literature review (part 1)

Literature Review Workflow (Adaptive Approach)

- **Adaptive Workflow**: An adaptive approach was taken to refine searches to balance completeness and feasibility.
- **Databases**: PubMed, MathSciNet, Scopus.
- **Search Terms**:
  - Core: uncertainty
  - Methods: Bayesian calibration, surrogate modeling, sensitivity analysis, etc.
  - Models: PBPK, QSP, ML.
- **Tools Used**:
  - Rayyan – abstract screening
  - Zotero – full-text retrieval
  - Elicit – data extraction
- **Outcome**: Organized dataset of UQ methods across PBPK/QSP/ML models.



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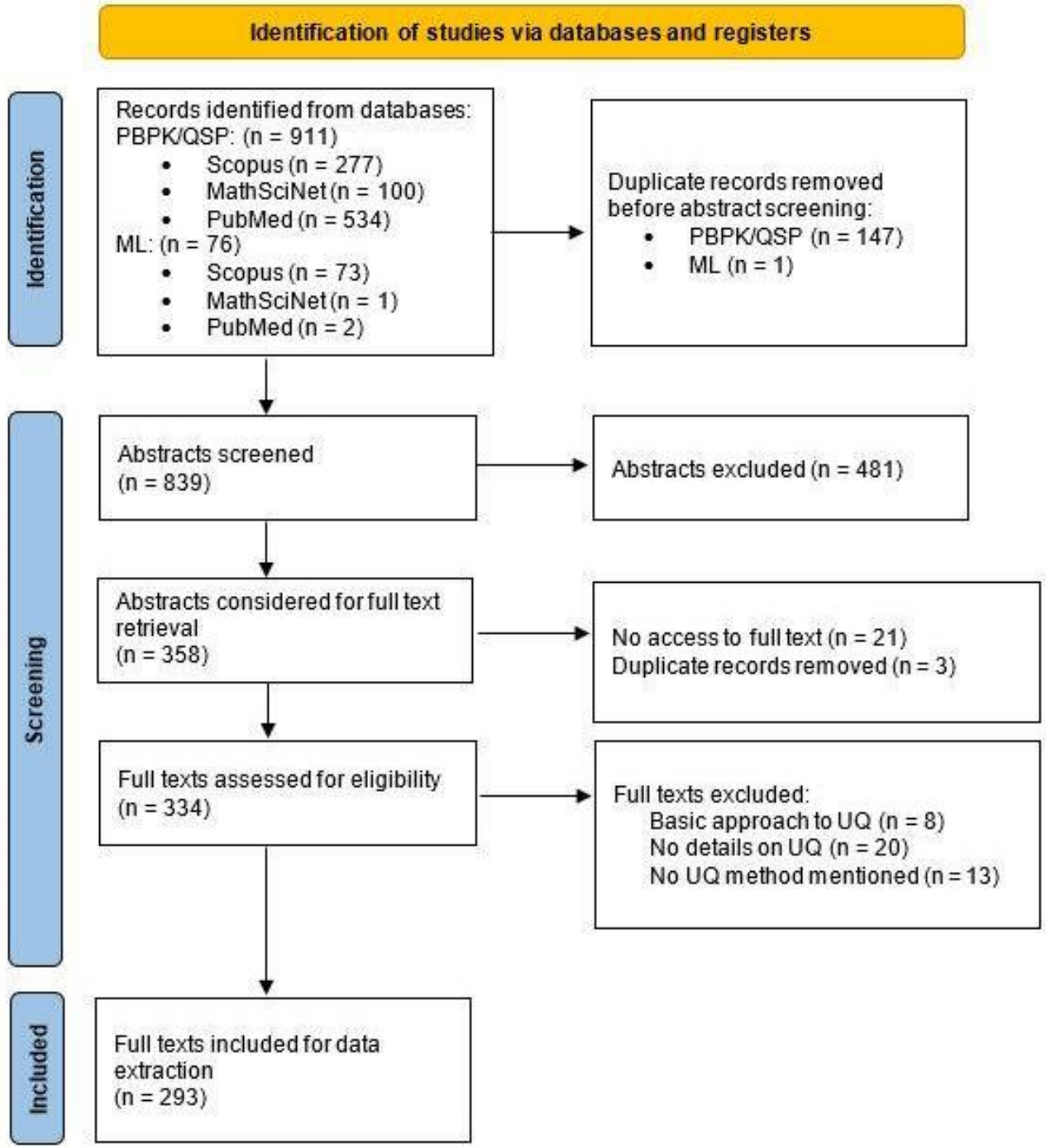
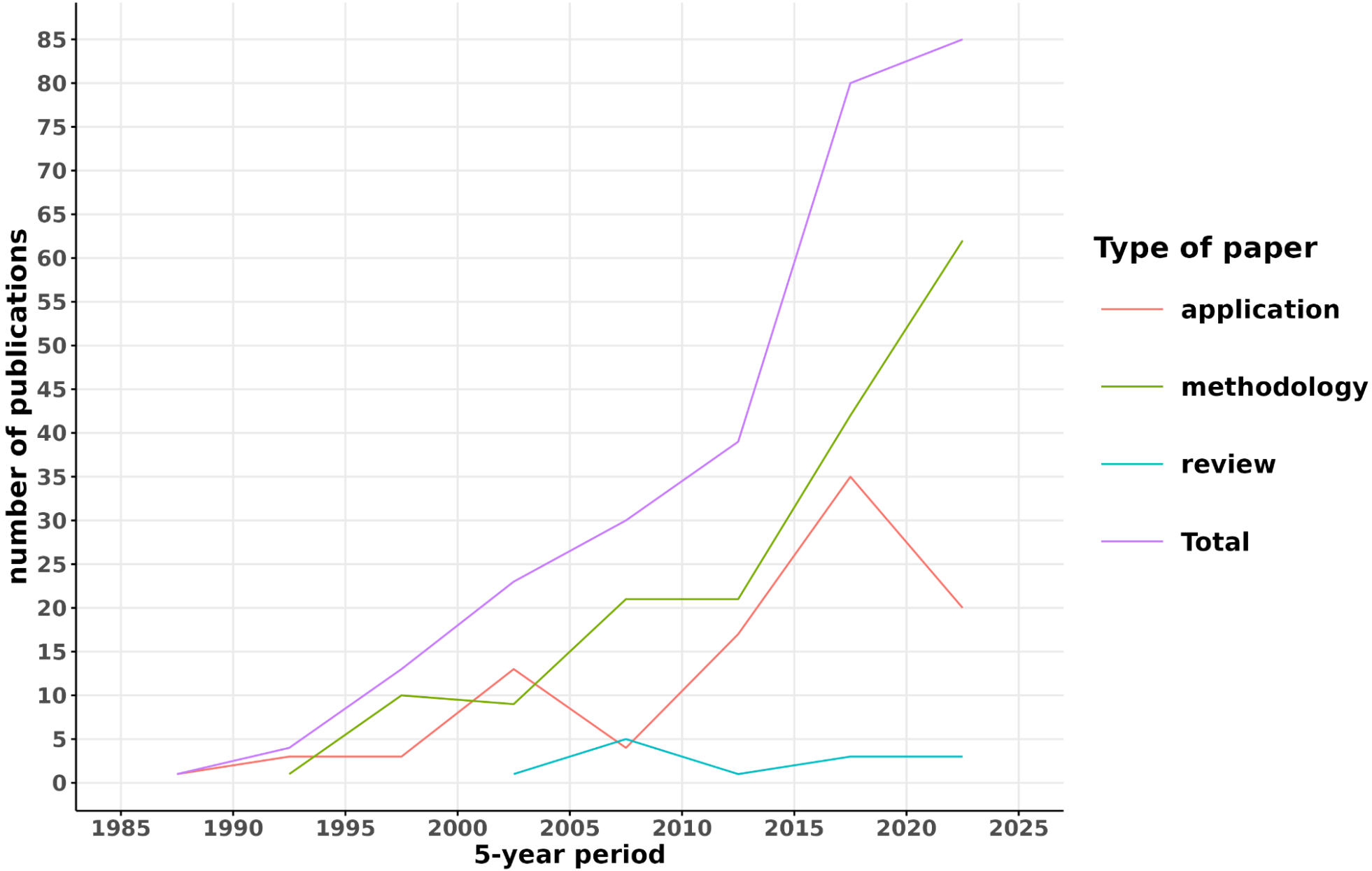
Search Strategy Details

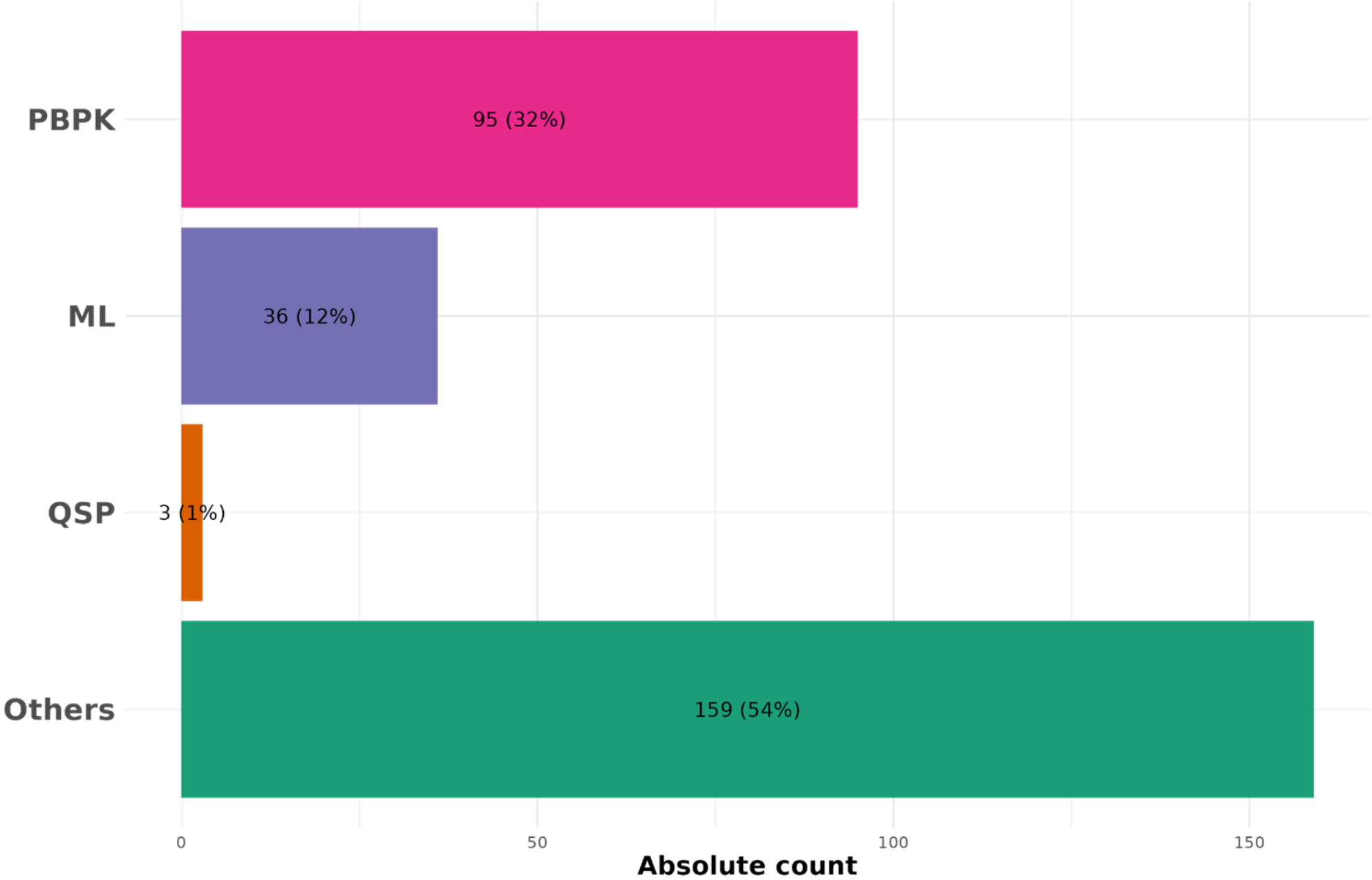
- **Databases & Keywords:**
  - PubMed, MathSciNet, Scopus
  - Combine UQ terms with PBPK/QSP/ML using “AND.”
- **Screening Process:**
  - Import results into Rayyan
  - Apply inclusion/exclusion criteria
  - Two reviewers screen independently; third resolves conflicts
- **Extraction Process:**
  - Retrieve full texts via Zotero
  - Use Elicit (AI tool) for initial extraction, followed by manual verification
  - Summarize results in Excel

PRISMA 2020 flow diagram





Type of complex model in included articles



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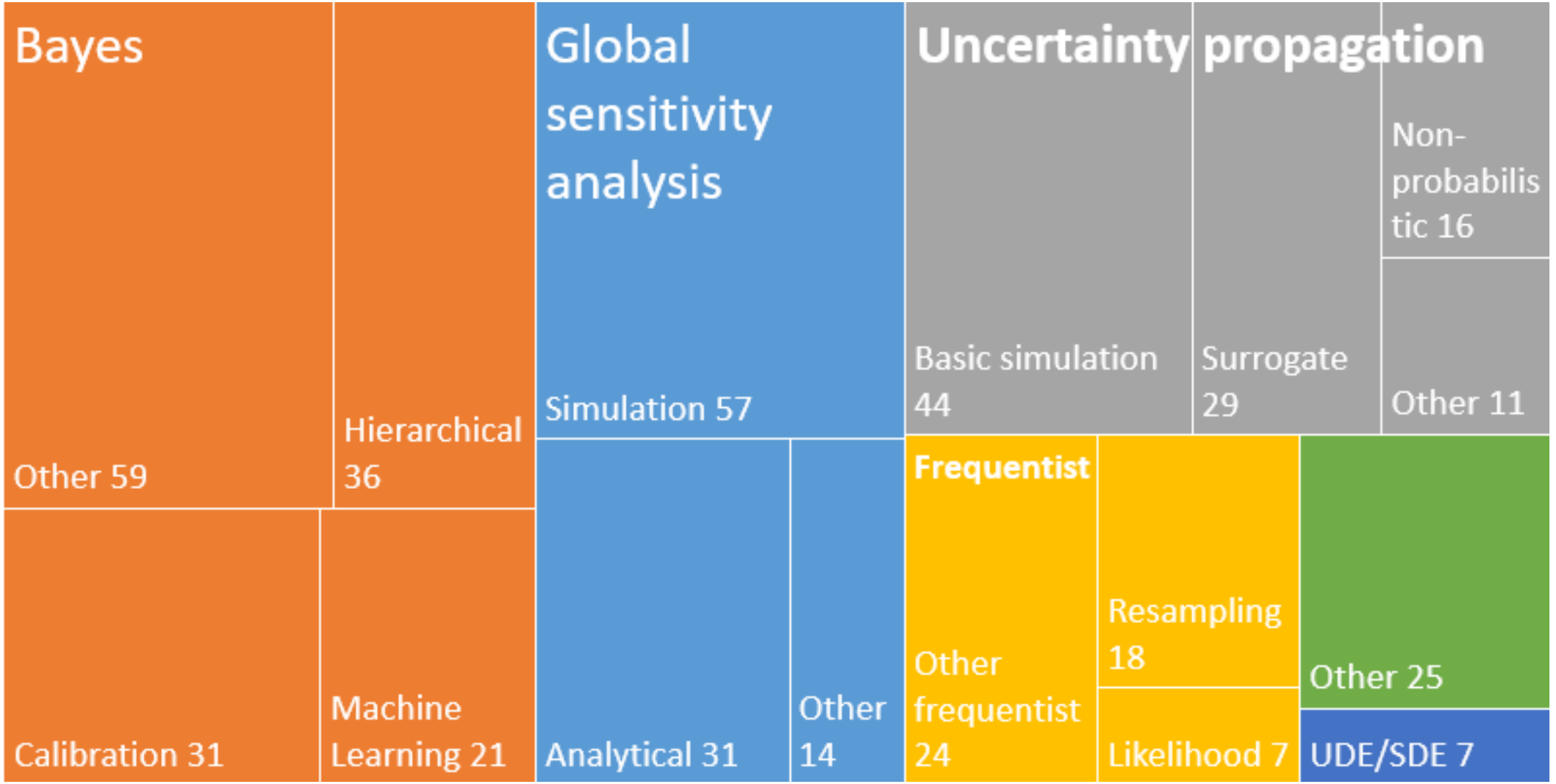
UQ methods in all included articles



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EPARS/SA review (part 2)

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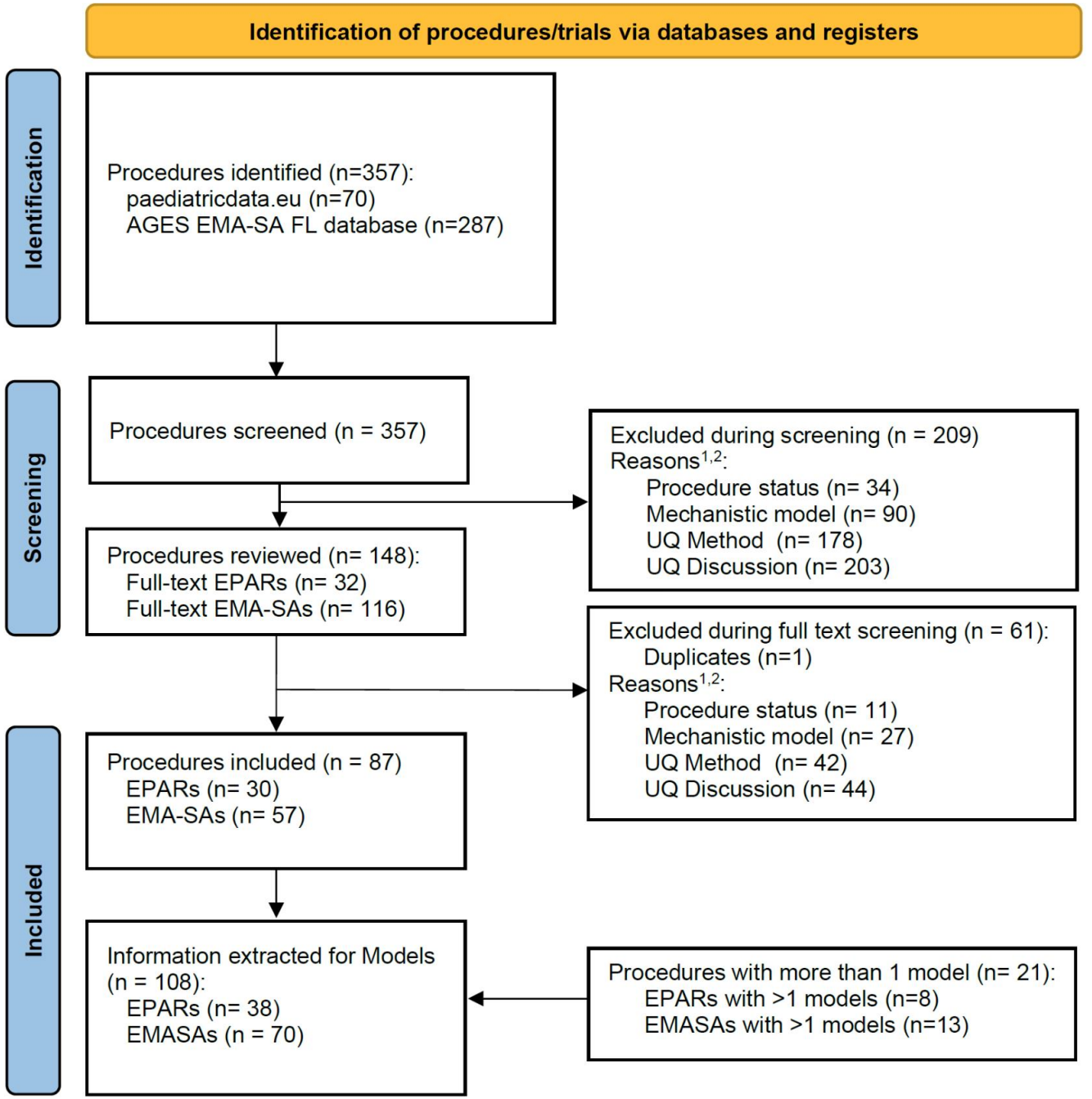
Search Strategy and Eligibility Criteria

- **Data Sources Utilized:** The review sourced information from EMA Public Assessment Reports and EMA Scientific Advice Final Letters databases.
- **Structured Search Method:** A structured search using predefined keywords focused on mechanistic modeling and uncertainty quantification was conducted.
- **Eligibility Criteria Defined:** Included procedures discussed mechanistic models and UQ methods before June 1, 2025; exclusions applied for lack of regulatory UQ discussion.
- **Data Screening and Analysis:** Screening and data extraction used standardized forms, followed by descriptive statistical analysis.

PRISMA 2020 flow diagram



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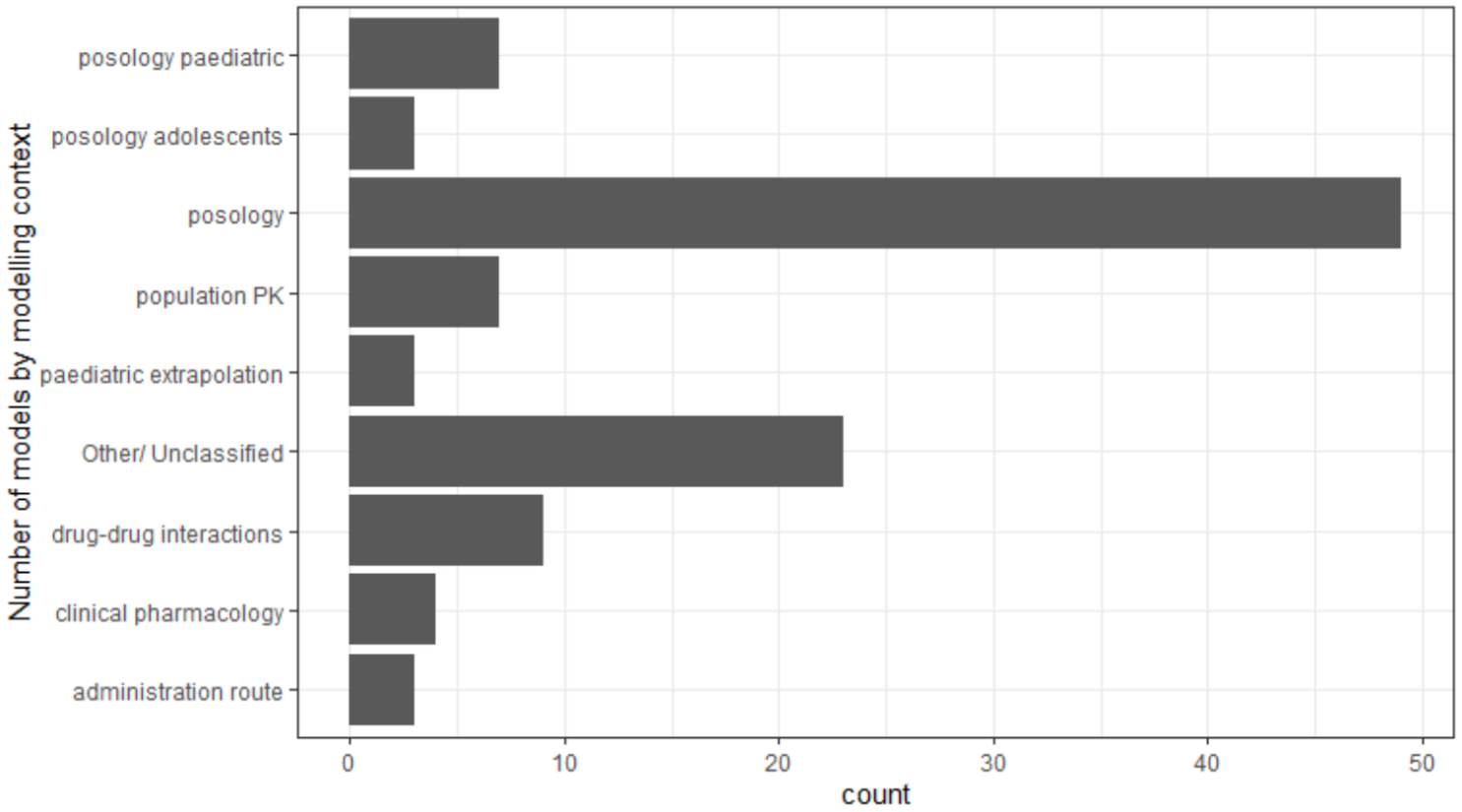
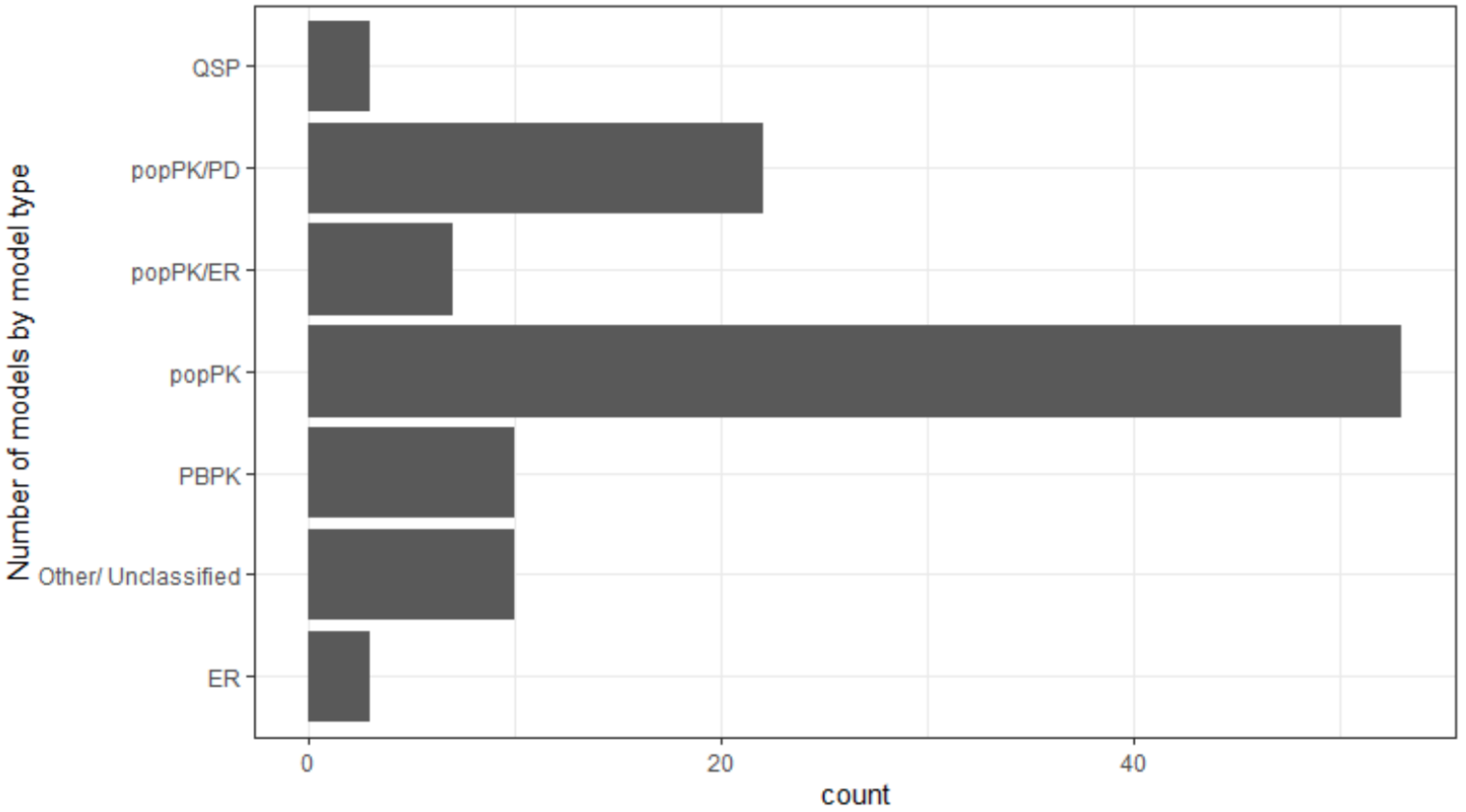
Number of models by modelling context



Number of models by type



Regulatory discussion

- Only brief discussion of UQ – 65%
- Reviewers were asked to assess whether the regulatory discussion indicated that UQ of the modelling approach—or the uncertainty reflected in the model results supported by various UQ methods—was considered adequate
  - Adequate - 50/108 (46%)
  - Unclear – 32/108 (30%)
  - Inadequate – 26/108 (24%)

Summary and Implications for Drug Development

- **Gap in UQ Methods**: There is a significant gap in well-established uncertainty quantification methods for complex drug development models.
- **Current UQ Practices in regulatory assessment**:
  - Uncertainty quantification in EMA regulatory procedures are often discussed at a high level without detail in the methods.
  - Findings highlight the necessity for standardized and comprehensive UQ methodologies in regulatory settings.
- **Promising UQ Techniques**: Techniques like global sensitivity analysis, uncertainty propagation, and Bayesian methods enhance model reliability and applicability.
- **Importance for Model Robustness**: Appropriate UQ methods improve the robustness of PBPK, QSP, and machine learning models in drug development.
- **Future Simulation Studies**: Future studies will refine UQ practices and support regulatory decision-making with robust evidence.

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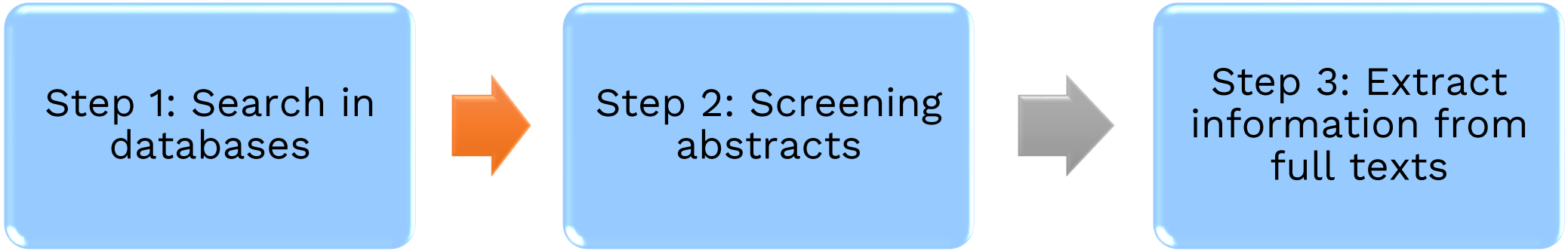
Acknowledgements and further reading

- EMA funding: FWC/EMA/2020/46/L3-ROC22-SC02

- Full report on this literature/EPAR/SA review can be found at: https://catalogues.ema.europa.eu/node/4620/administrative-details

Literature review workflow



Database Searching Methodology: Structured searches used PubMed, MathSciNet, and Scopus with refined keywords and fuzzy search techniques for best coverage and relevance.

Screening and Selection Process: Abstracts were screened using Rayyan software with clear inclusion and exclusion criteria for relevant paper selection.

Full-Text Extraction and Data Organization: Full texts were retrieved via Zotero and data extracted using AI tools (Elicit), then organized into detailed spreadsheets for accuracy.

Manual Verification Ensures Accuracy: Manual checks were performed to verify data accuracy and properly categorize papers and uncertainty quantification methods.

Step 1: Search in databases

- **Databases**
  - PubMed (for medical field)
  - MathSciNet (mathematics & statistics)
  - Scopus (wide ranges of topic)
- **Structured search terms:**
  1. **Uncertainty quantification/analysis**
     - **core term:** uncertainty
     - **specific methods:** Bayesian hierarchical meta-regression, Bayesian calibration, model discrepancy analysis, surrogate modeling, probabilistic sensitivity analysis, uncertainty propagation, interval analysis, fuzzy computations, frequentist.
  2. **Complex models**
     - **PBPK & QSP related models:** Physiologically based pharmacokinetic modeling (PBPK), Physiologically based biopharmaceutics modeling (PBBM), Quantitative systems pharmacology (QSP), PBPK model used in toxicology (study toxin instead of drugs), Quantitative Systems Toxicology (QST)
     - **Machine learning (ML) models**
  3. **Use "AND" for the above two fields**

Quality control:

Check that the resultant search includes the following papers and results in a feasible number of papers to review, if not, redefine search terms.

1. Kennedy MC, O'Hagan A. Bayesian calibration of computer models. Journal of the Royal Statistical Society Series B: Statistical Methodology. 2001;63:425–64
2. Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. International Journal of Epidemiology. 2014;43:1969–85
3. Strong M, Oakley JE. When is a model good enough? Deriving the expected value of model improvement via specifying internal model discrepancies. SIAM/ASA Journal on Uncertainty Quantification. 2014;2:106–25
4. Owen, N. E., Challenor, P., Menon, P. P., & Bennani, S. (2017). Comparison of surrogate-based uncertainty quantification methods for computationally expensive simulators. SIAM/ASA Journal on Uncertainty Quantification, 5(1), 403-435.

Step 2: Screening abstracts & Criteria

- Import search results into **Rayyan** for screening.
- Apply inclusion/exclusion criteria.
- Two reviewers screen independently; third resolves conflicts.
- **Inclusion**: UQ methods, case studies (PBPK, QSP, ML), other relevant models.
- **Exclusion**: Not relevant to UQ, UQ only for estimation (e.g., local sensitivity), or full text unavailable.

Step 3: Extract information from full texts: **general procedures**

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- Retrieve Full Texts

Access papers via ***Zotero***→ Exclude those without full text access at Uppsala University or University Medical Center Göttingen and remove duplicates.

- Information Extraction

Use ***Elicit*** for initial data extraction, define and train the instructions for the columns on 10 papers and apply on all papers.

- Manual Verification

Check extracted information from all papers manually. If ***Elicit*** is wrong, the information will be corrected manually.

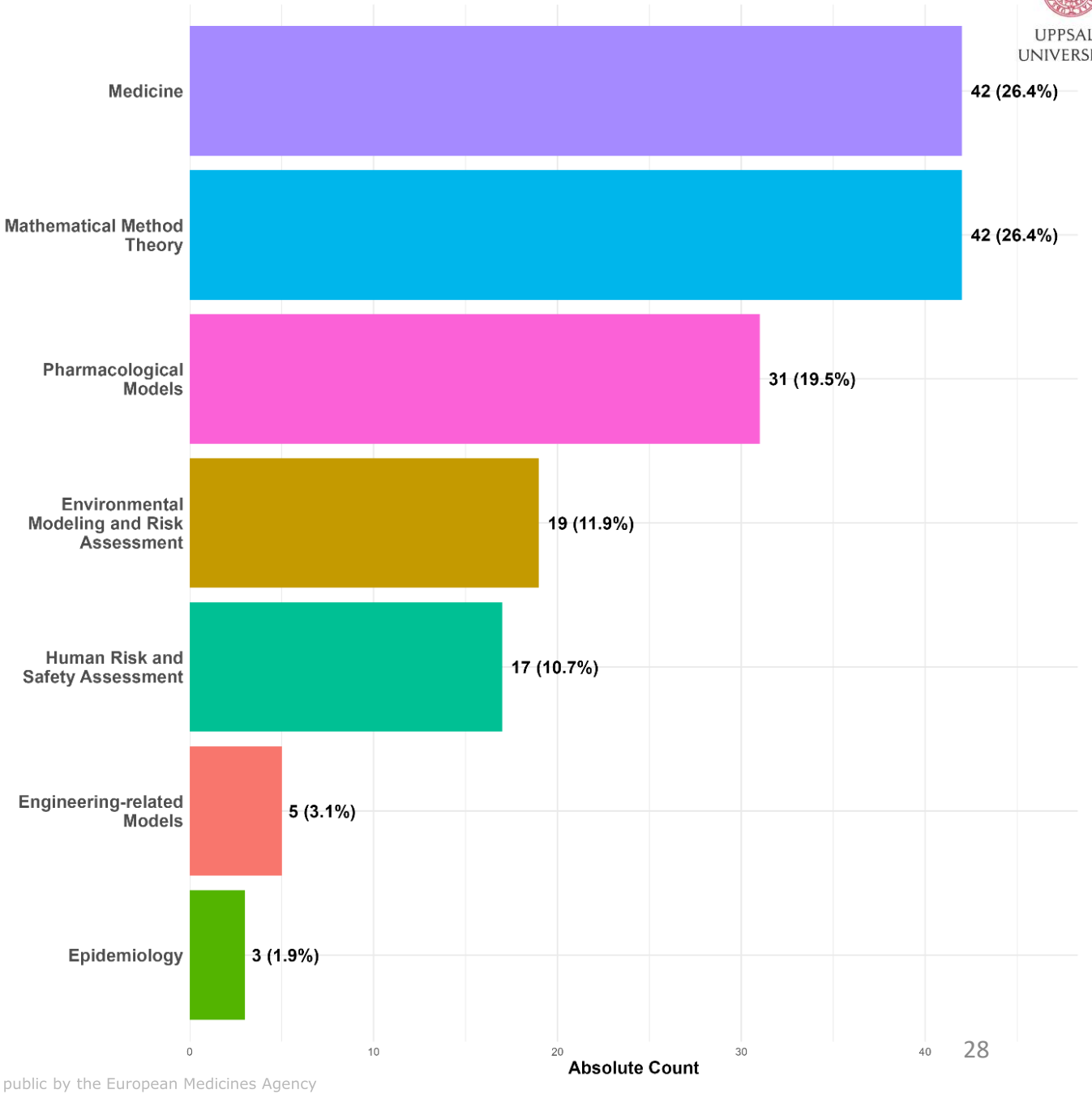
- Summarize results via ***Excel***.

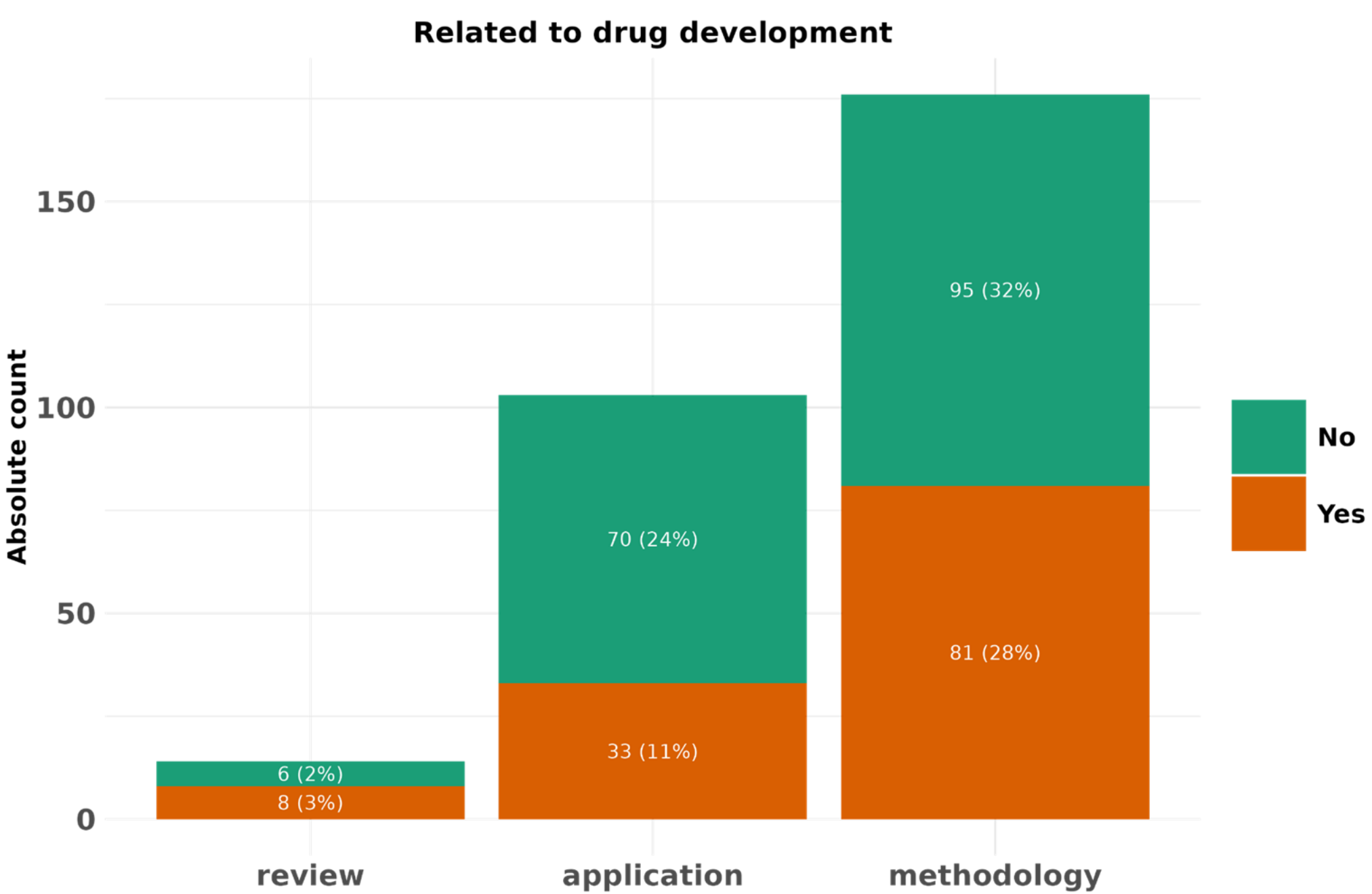
Step 3: Extract information from full texts: **Information to extract**

Search results are organized in a table with following 20 columns:

- ID
- Title
- Authors
- Source/Journal
- Year
- DOI/Full Text link
- Inclusion? (yes/no)
    - If no inclusion, reason
- Type of paper (Methodology/Application/Review)
- **Type of model (PBPK/QSP/ML/Others)**
- **UQ methods**
- **If it is related to drug development**
    - Purpose of the model
    - Type of the product : small molecule, biologics
    - Therapeutic area
    - Stage of drug development
- **Simulation? (yes/no)**
- Software availability? (Open source/Commercial/Open source+Commercial/No)
- Software used
- Code availability? (Open source/Commercial platform with given parameters/upon the request to the authors/No)
- Comments

Absolute number of articles by type of models in the “Others” category (n=159)



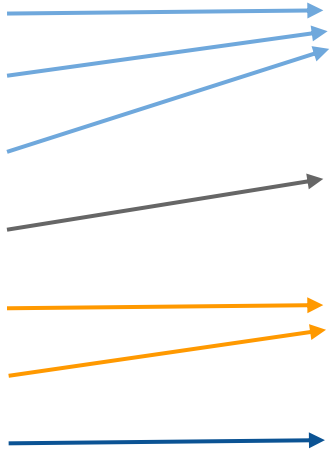


Categorisation Uncertainty Quantification methods

- Screening process without predefined classification of all UQ methods
- Extraction of specific method names and general keywords like sensitivity analysis and uncertainty propagation

List of methods and keywords

- Morris method
- Monte Carlo simulation
- Polynomial Chaos Expansion
- Fuzzy computation
- Monte Carlo dropout
- Bayesian hierarchical modeling
- Uncertain differential equations
- …



Categorisation

- Global sensitivity analysis
- Uncertainty propagation
- Bayesian methods
- UDE/SDE
- …

Categorisation Uncertainty Quantification methods

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List of methods and keywords

- Morris method
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- Polynomial Chaos Expansion
- Monte Carlo dropout
- Bayesian hierarchical modeling
- …

Categorisation

- Global sensitivity analysis
  - Simulation-based
  - Analytical
  - …
- Bayesian methods
  - Bayesian ML
  - Hierarchical modeling
  - …

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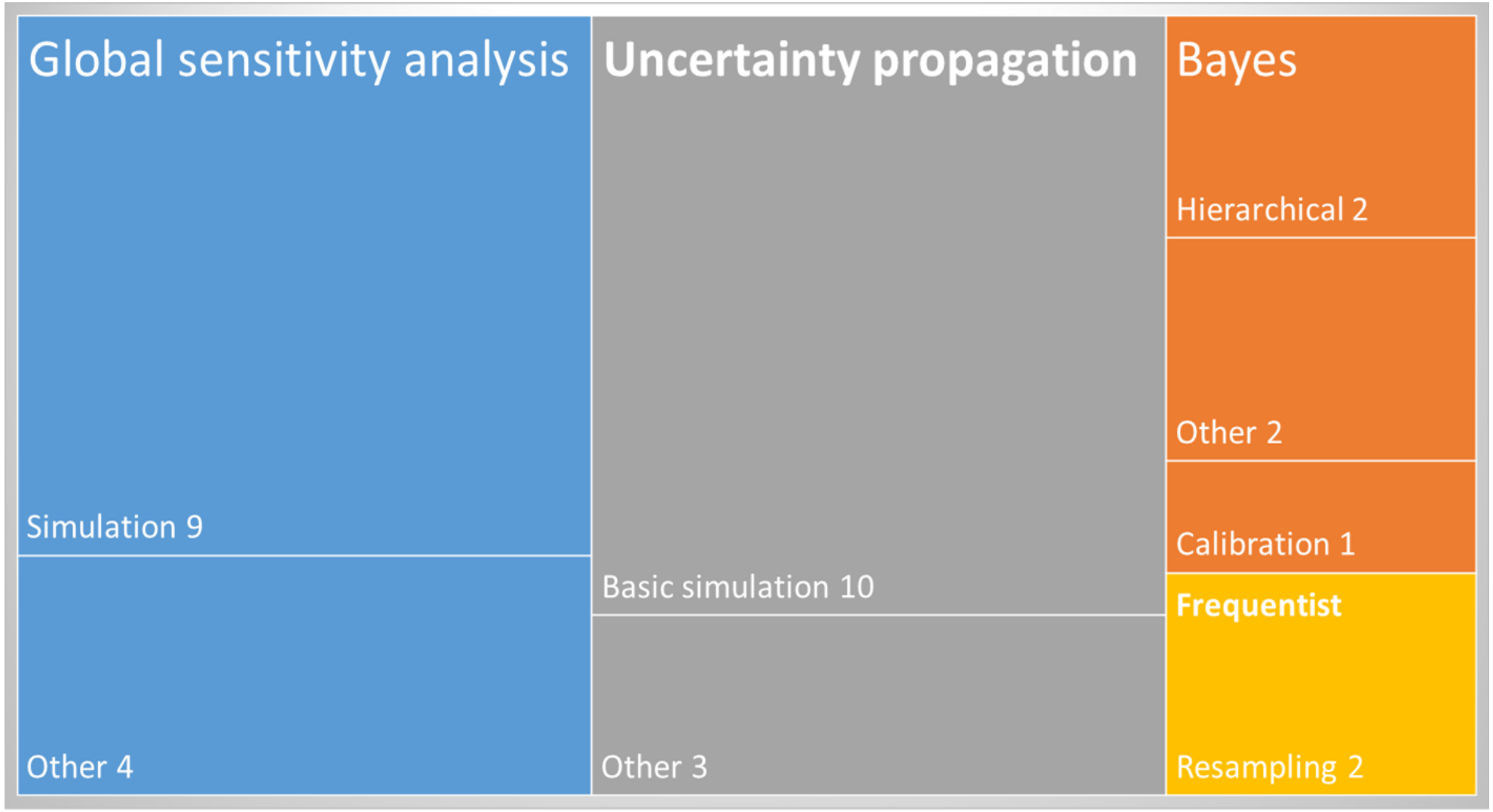
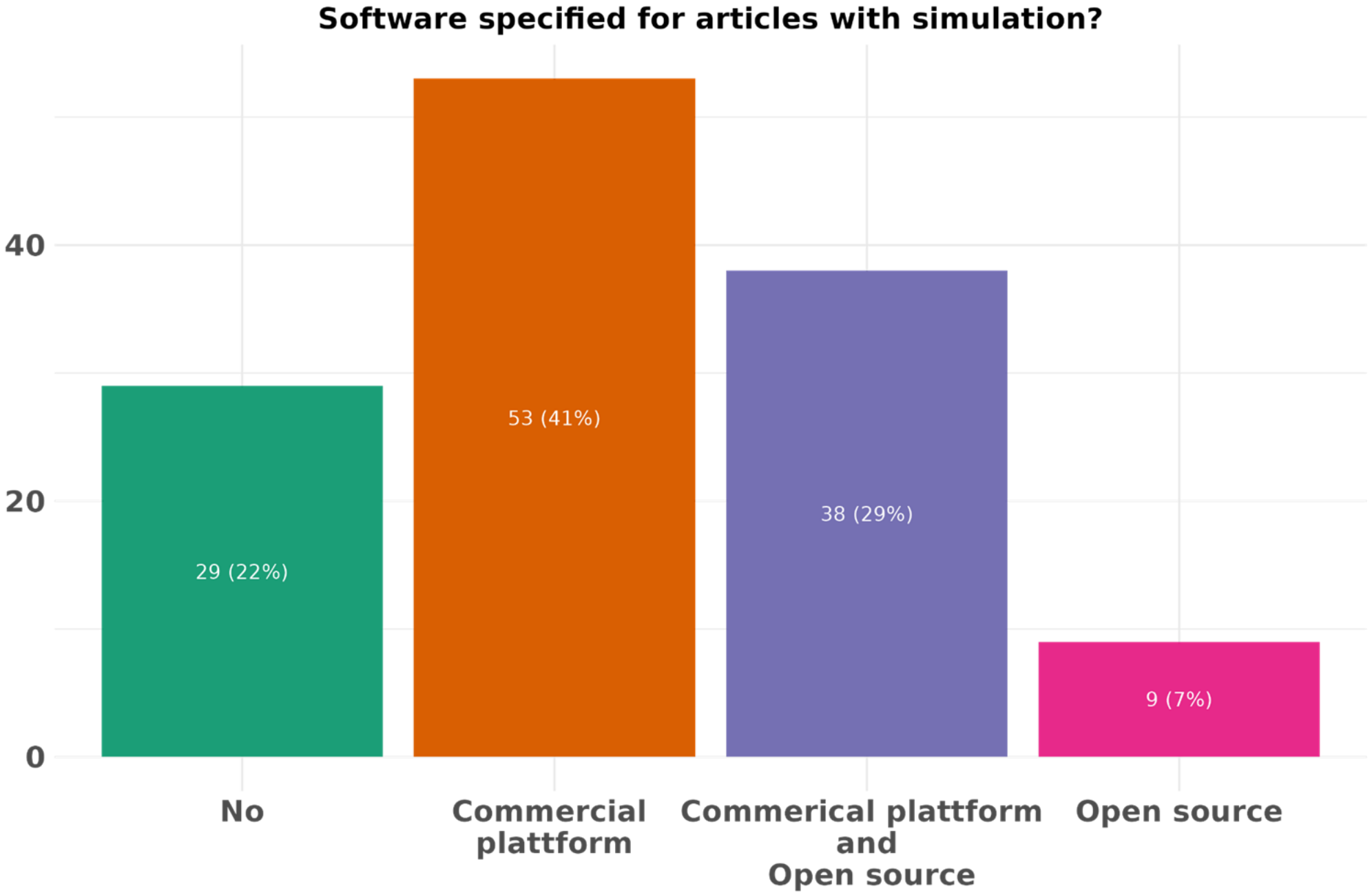
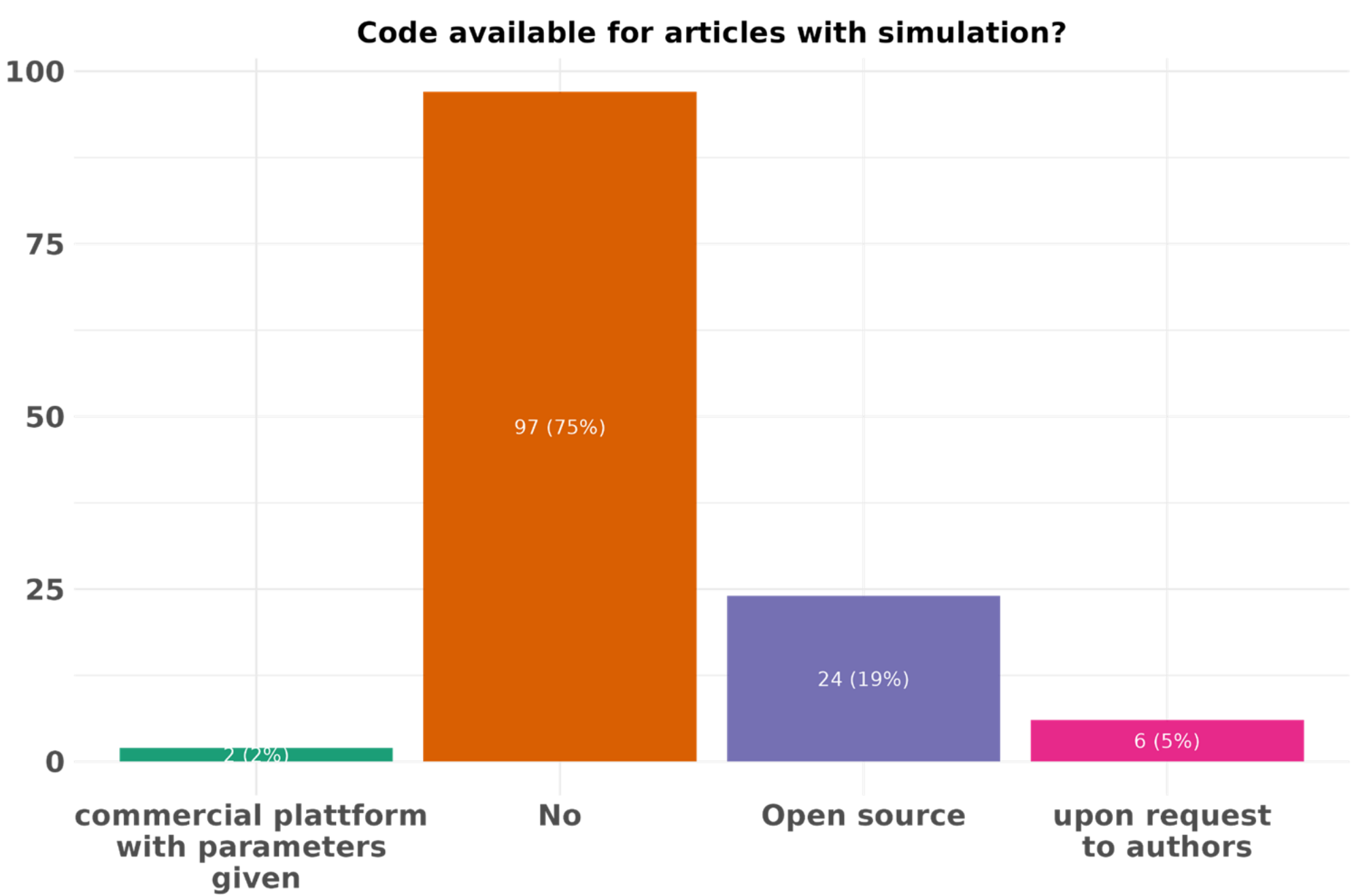
UQ methods for PBPK/QSP models since 2015







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