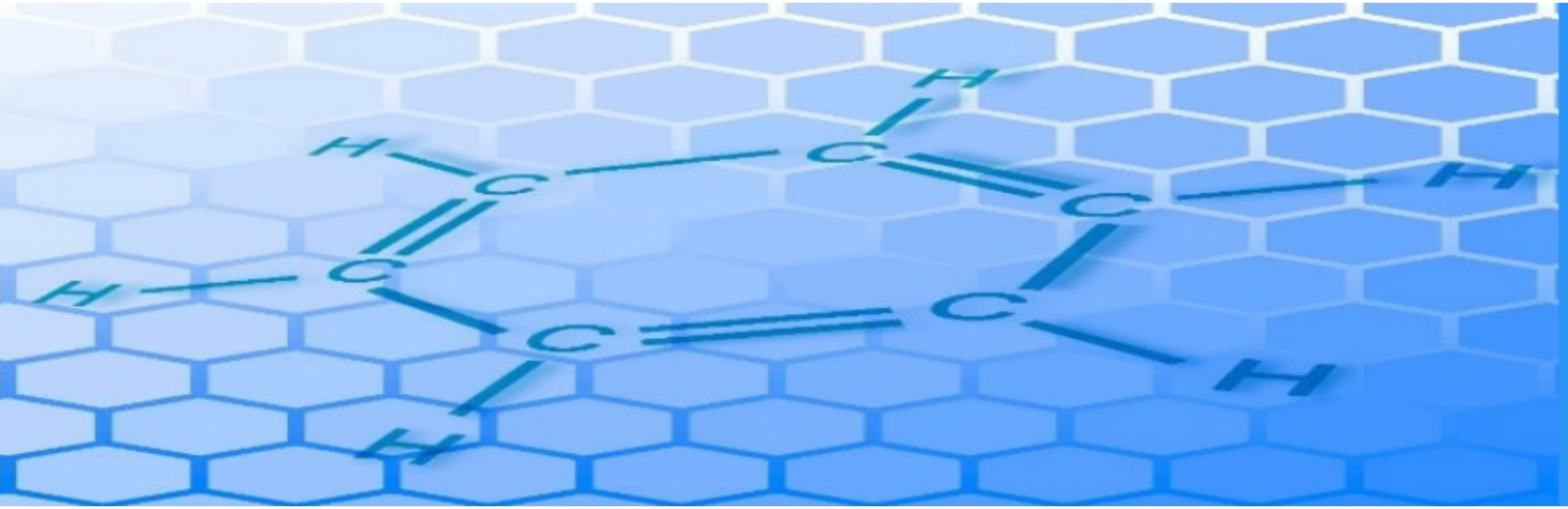
Aromatics Producers Association (APA)

A sector group of Cefic
European Chemical Industry Council - Cefic aisbl

Quality assessment of human observational studies of chemical exposure

Maurice Zeegers



APA Symposium

Helsinki, Finland

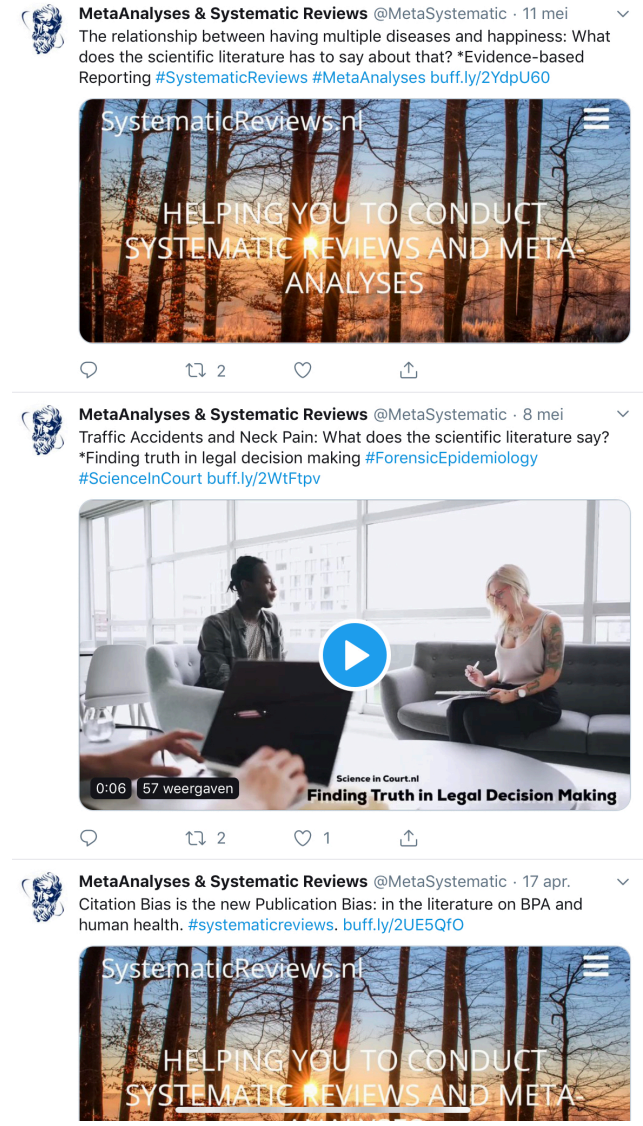
11 September 2019

Aromatics Producers Association (APA)

www.epicurus-reviews.com

CONFLICT OF INTEREST

1. Professor at Maastricht University (Complex Genetics and Epidemiology)
2. Epicurus-reviews.com
3. Commensuration via CEFIC – APA
4. Textbook of Epidemiology (Bouter, Zielhuis, Zeegers)



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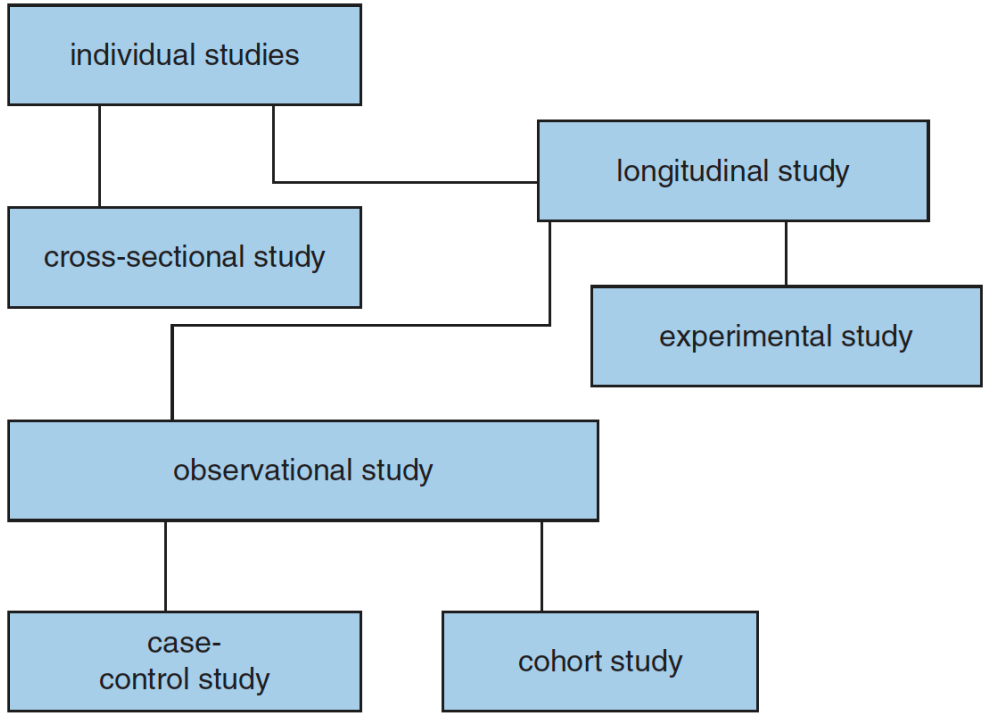
EPIDEMIOLOGY (AND WHY IS IT IMPORTANT)

Focus on Human Observational Studies

1. Limited extrapolation is needed (Real World Evidence)
2. Different Study Designs
3. Evaluation of Quality is essential for Quantitative Risk Assessment



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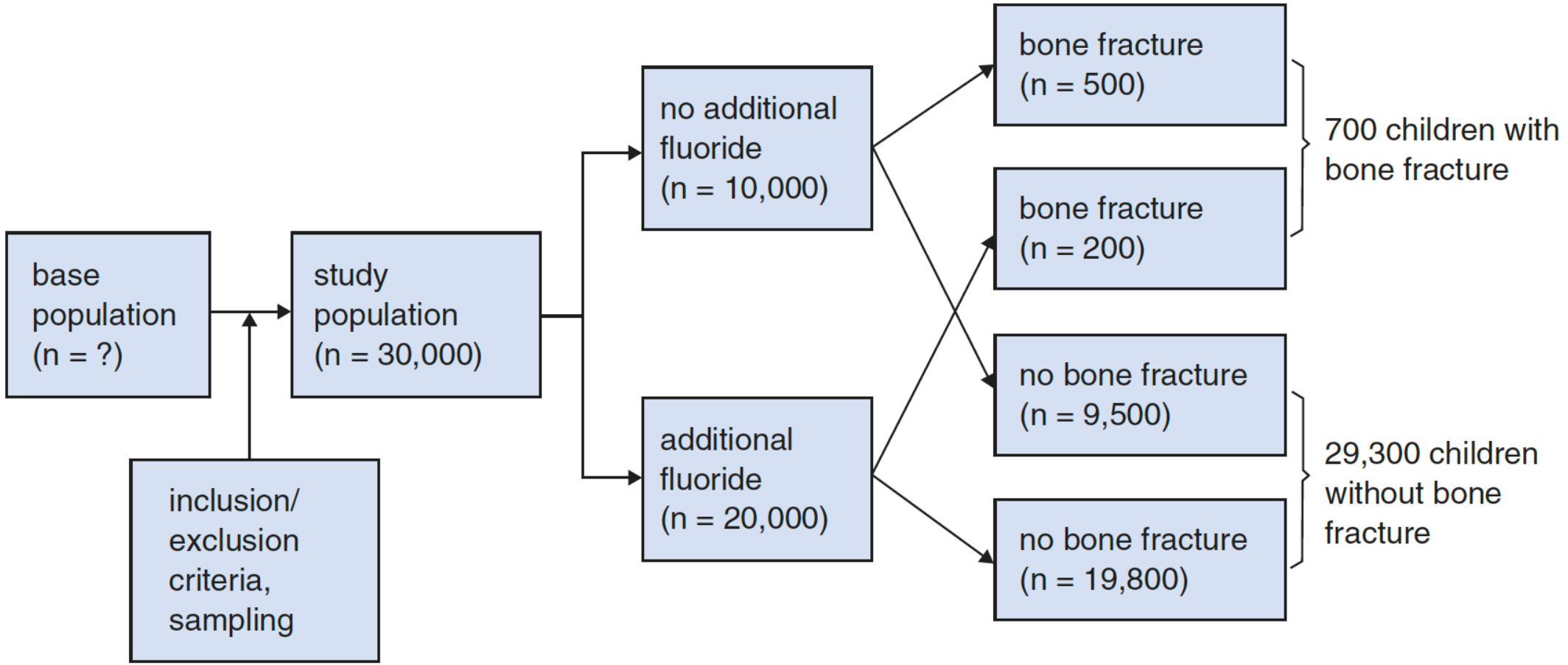

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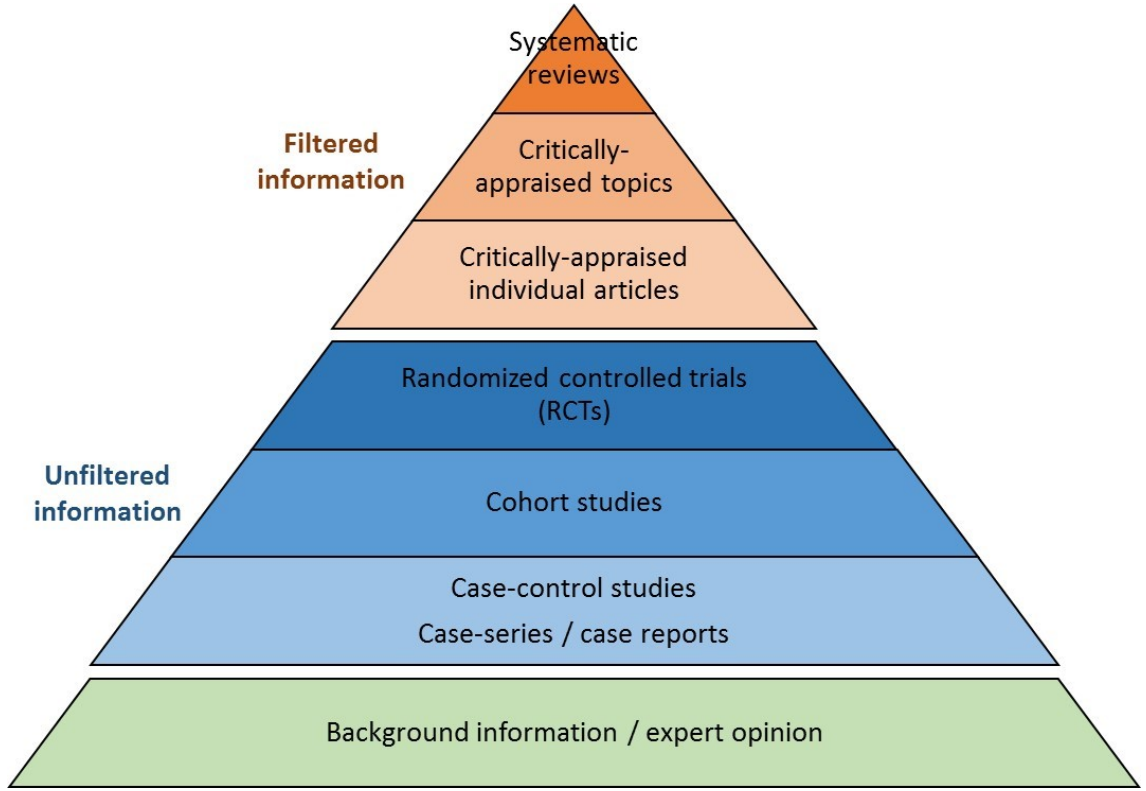
SYSTEMATIC REVIEW (AND WHY IS IT IMPORTANT)

1. Formulate the Research Questions
2. Identify the Component Studies
3. Extraction of Study Characteristics (Today's focus)
4. Extraction of Study Results
5. Statistical Analyses (in case of Meta-Analyses)
6. Reporting (Application to Society)



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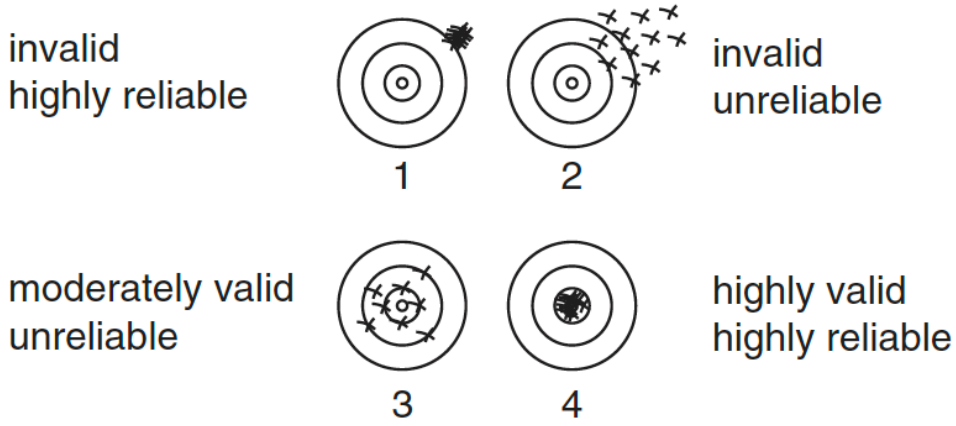

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QUALITY ASSESSMENT (OF HUMAN OBSERVATIONAL STUDIES)

Quality of Individual Studies

1. Risk of Bias for an Individual Human Observational Study (New Castle – Ottawa)
2. Risk of Bias for Multiple Human Observational Studies for Quantitative Risk Asessment (Vlaanderen List)

Quality of Systematic Reviews

1. Quality of Reporting (PRISMA)
2. Risk of Bias (ROBIS)

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DATABASES USED FOR SYSTEMATIC REVIEWS

- Pubmed
- Scholar Google
- Science Direct
- Web of Science
- Scopus
- Journal Citation Reports
- Research Gate
- Index Chemicus
- KSR Evidence
- Cochrane Library

REPORTING CHECKLISTS

- Quality: Observational studies
- Quality: Observational Studies for Risk Assessment
- Reporting: Observational studies
- Quality: Diagnostic studies
- Reporting: Diagnostic studies
- Quality: Randomised Intervention Studies
- Quality: Non-Randomised Intervention Studies
- Reporting: Intervention studies
- Quality: Systematic Reviews of RCTs
- Quality: Systematic Reviews
- Reporting: Systematic Reviews
- Levels of Evidence (GRADE)

RECENT PUBLICATIONS

Impact of changes in human reproduction on the incidence of endocrine-related diseases (Critical Reviews Toxicology 2018)

Selective citation in scientific literature on the human health effects of bisphenol A (Research Integrity and Peer Review 2019)

The strong focus on positive results in abstracts may cause bias in systematic reviews: a case study on abstract reporting bias (Systematic Reviews 2019)

Selective citation in the literature on the hygiene hypothesis: a citation analysis on the association between infections and rhinitis (BMJ Open 2019)

Citation bias in the literature on dietary trans fatty acids and serum cholesterol (Journal of Clinical Epidemiology 2019)

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MetaAnalyses & Systematic Reviews
@MetaSystematic

Abstract Reporting Bias is the new Publication Bias
buff.ly/30Lsf9A #SystematicReviews #MetaAnalyses
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THE NEW CASTLE-OTTAWA SCALE (CASE-CONTROL STUDIES)

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

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THE NEW CASTLE-OTTAWA SCALE (COHORT STUDIES)

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

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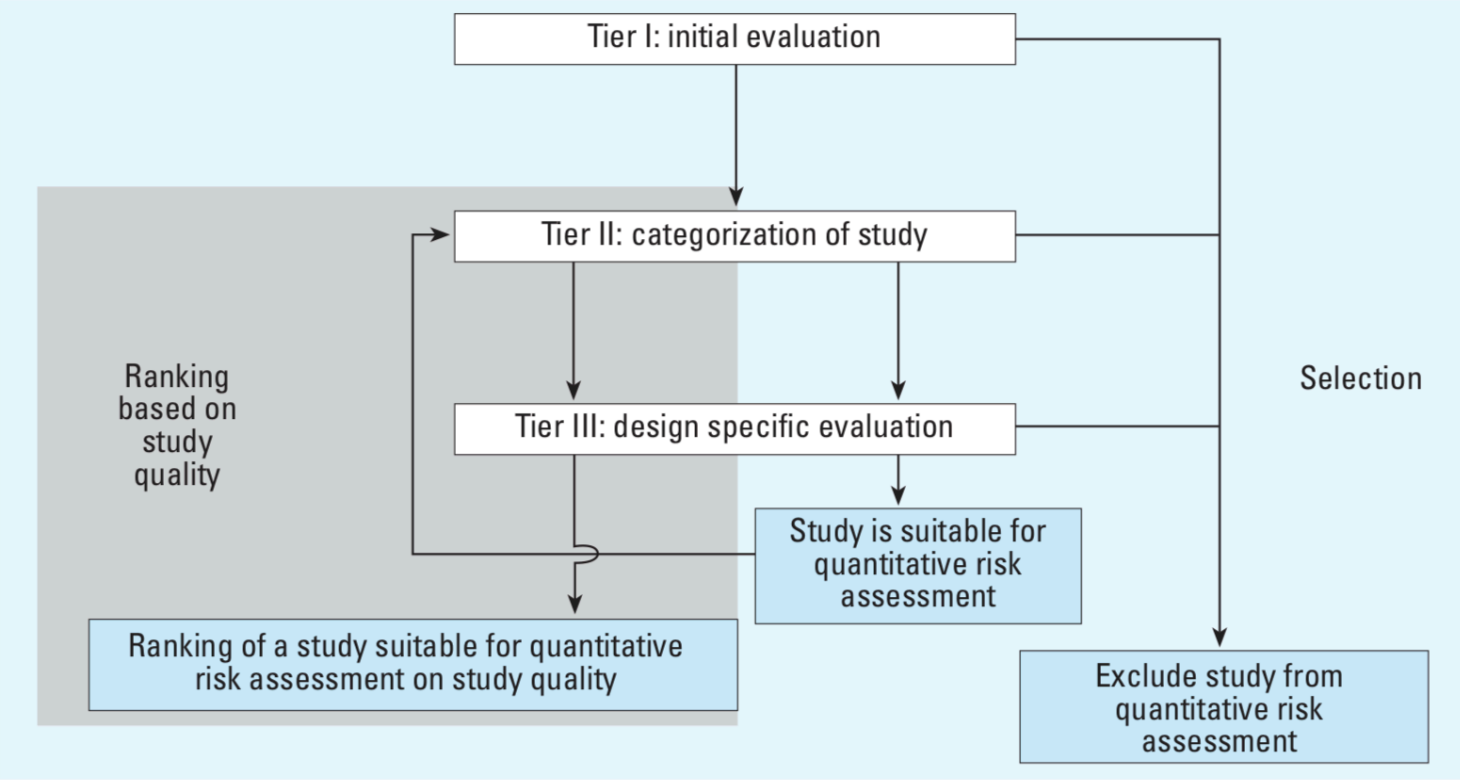
THE VLAANDEREN LIST



THE VLAANDEREN LIST

Tier	Evaluation criteria	Outcome	Impact on evaluation	CC[b]	COH[c]	CR[d]
I[e]	1.1 Is the study design case–control, cohort, or cross-sectional?	Yes/no	Selection for QRA[f]	X	X	X
I[e]	1.2 Is exposure expressed on a ratio scale and specific for the agent of interest?	Yes/no	Selection for QRA[f]	X	X	X
I[e]	1.3 Is a detailed description of the statistical analysis provided?	Yes/no	Selection for QRA[f]	X	X	X
I[e]	1.4 Are criteria for inclusion of subjects into the study described with sufficient detail?	Yes/no	Selection for QRA[f]	X	X	X
I[e]	1.5 Is the assessment of the health effect performed according to recognized norms?	Yes/no	Selection for QRA[f]	X	X	X
I[e]	1.6 Are all relevant potential strong confounding factors considered in the study design?	Yes/no	Selection for QRA[f]	X	X	X
II[g]	2.1 Type of study design	Case–control/cohort/ cross-sectional	Selection for QRA[f]/ study quality ranking[h]	X	X	X
III[i]	3.1 Response rate	Numerical	Selection for QRA[f]/ study quality ranking[h]	X	X	X
III[i]	3.2 Loss to follow-up	Numerical	Selection for QRA[f]/ study quality ranking[h]		X	
III[i]	3.3 Minimum follow-up time	Description	Selection for QRA[f]		X	
III[i]	3.4 Quality of the exposure measurement methods	Description	Selection for QRA[f]/ study quality ranking[h]	X	X	X
III[i]	3.5 Insight in the variability of exposure	Description	Study quality ranking[h]	X	X	X
III[i]	3.6 Application of exposure measurements in exposure assessment	Description	Selection for QRA[f]/ study quality ranking[h]	X	X	X
III[i]	3.7 Type of exposure metric	Description	Study quality ranking [h]	X	X	X
III[i]	3.8 Specificity of the exposure indicator	Category[j]	Study quality ranking [h]	X	X	X
III[i]	3.9 Blinded exposure assessment	Description	Selection for QRA[f]	X	X	X
III[i]	3.10 Quality of the exposure assignment strategy	Description	Study quality ranking [h]	X	X	
III[i]	3.11 Potential for information bias	Description	Study quality ranking [h]	X	X	X
III[i]	3.12 Blinded health outcome assessment?	Description	Selection for QRA[f]		X	X
III[i]	3.13 Insight in the potential for systematic error in study results	Description	Study quality ranking [h]	X	X	X

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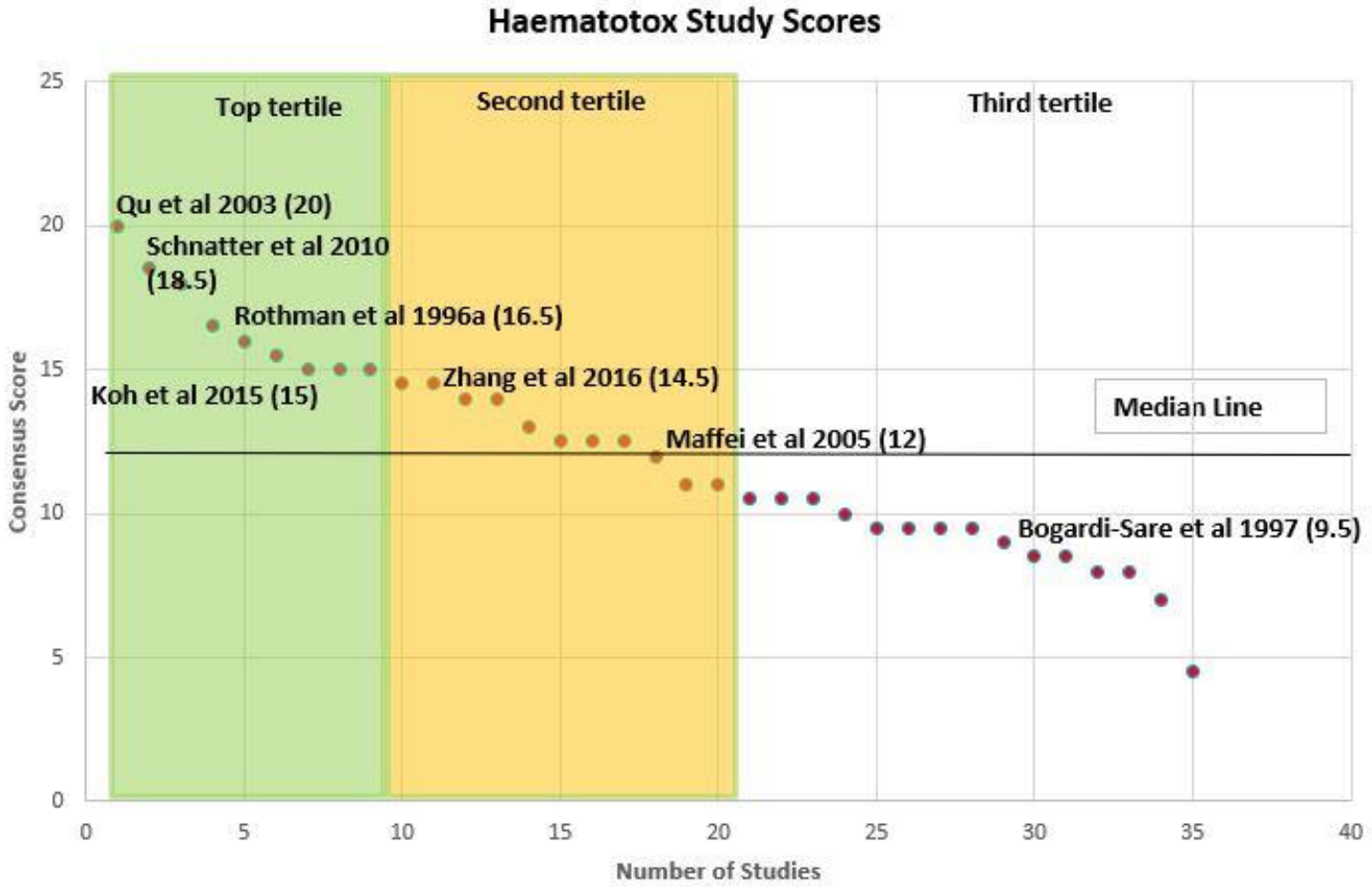

PRISMA (PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. Protocol exists however at CEBM website	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Data 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

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PRISMA (PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 2-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 2-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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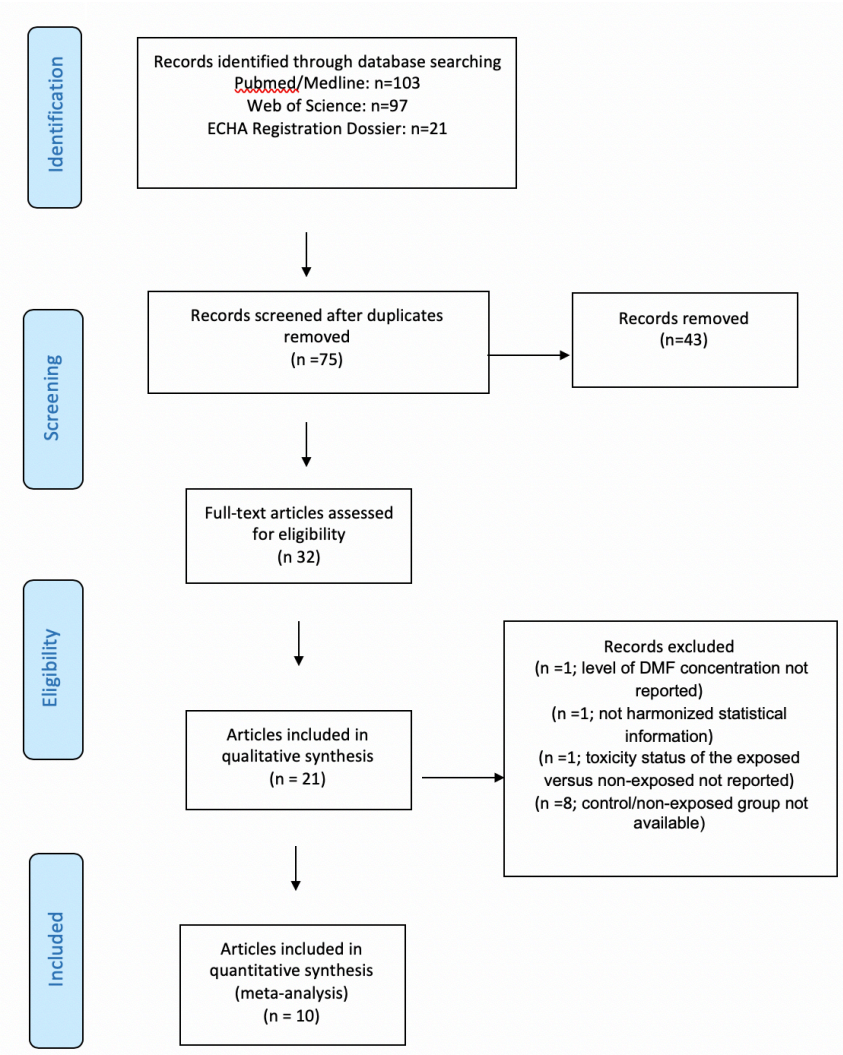
PRISMA (FLOW CHART)



ROBIS (RISK OF BIAS IN SYSTEMATIC REVIEWS)

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):	Adult women with suspected pregnancy in the UK	European, USA and Canada
Exposure(s) and comparator(s):	Exposure to Oral Hormone Pregnancy Tests (HTPs), specifically Primodos and Amenorone Forte	Exposure to HTPs, including Primodos and Amenorone Forte
Outcome(s):	Range of congenital abnormalities, including VACTR	Abnormalities organised by tract, including VACTR

ROBIS (RISK OF BIAS IN SYSTEMATIC REVIEWS)

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

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ROBIS (RISK OF BIAS IN SYSTEMATIC REVIEWS)

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies Rationale for concern:	LOW/HIGH/UNCLEAR

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ROBIS (RISK OF BIAS IN SYSTEMATIC REVIEWS)

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

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ROBIS (RISK OF BIAS IN SYSTEMATIC REVIEWS)

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

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ROBIS (RISK OF BIAS IN SYSTEMATIC REVIEWS)

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	No	
2. Concerns regarding methods used to identify and/or select studies	No	
3. Concerns regarding methods used to collect data and appraise studies	No	
4. Concerns regarding the synthesis and findings	Yes	Low quality & limited power in primary studies

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review	RISK: LOW/HIGH/UNCLEAR
Rationale for risk:	

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CAUSALITY (QUANTITATIVE RISK ASSESSMENT)

- Association Measurements
- Pooled Estimates
- Probability of Causation

	O	$\bar{O}$		
D	n_1		N_1	$CI_1 = n_1 / N_1$
$\bar{D}$	n_0		N_0	$CI_0 = n_0 / N_0$
	n_T		N_T	$CI_T = n_T / N_T$

$$RR = \frac{CI_1}{CI_0} = CI$$

$$AR = CI_1 - CI_0 = CID$$

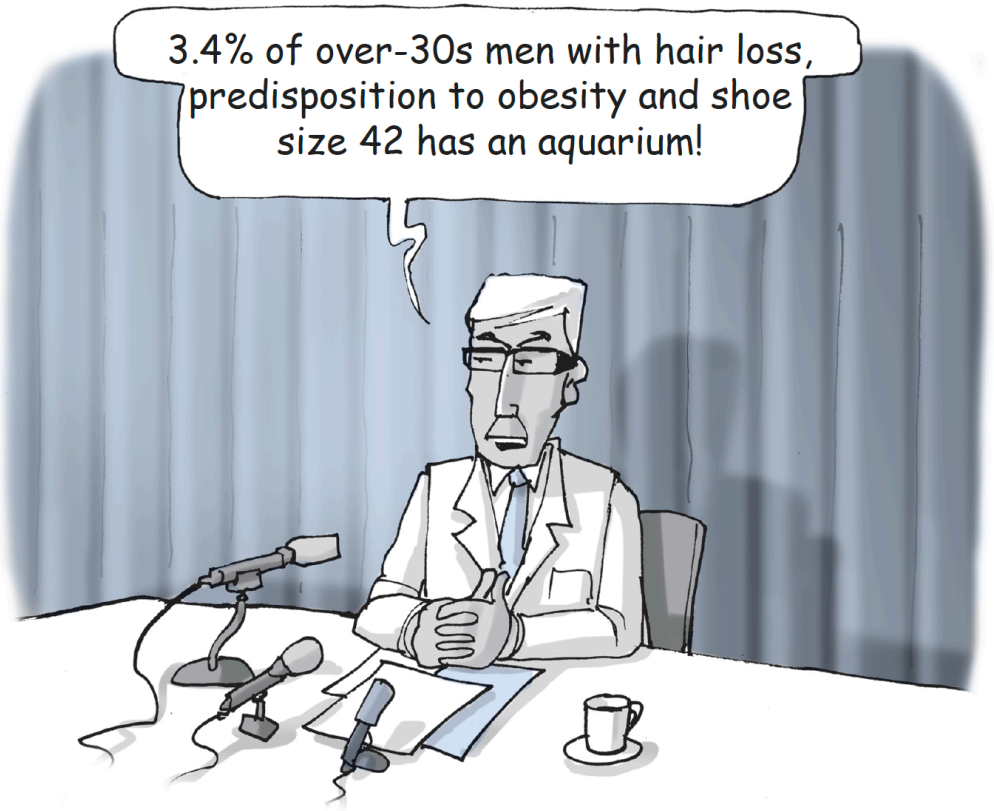
$$EF_e = \frac{CI_1 - CI_0}{CI_1} = 1 - 1 / CIR$$

$$PAR = \frac{CI_T - CI_0}{CI_T} = \frac{p(CIR-1)}{p(CIR-1) + 1}$$

$$p = N_1 / N_T$$

CAUSALITY (CRITERIA)

- Strength
- Consistency
- Specificity
- Temporal sequence
- Dose response
- Experimental evidence
- Biological plausibility
- Coherence
- Analogy



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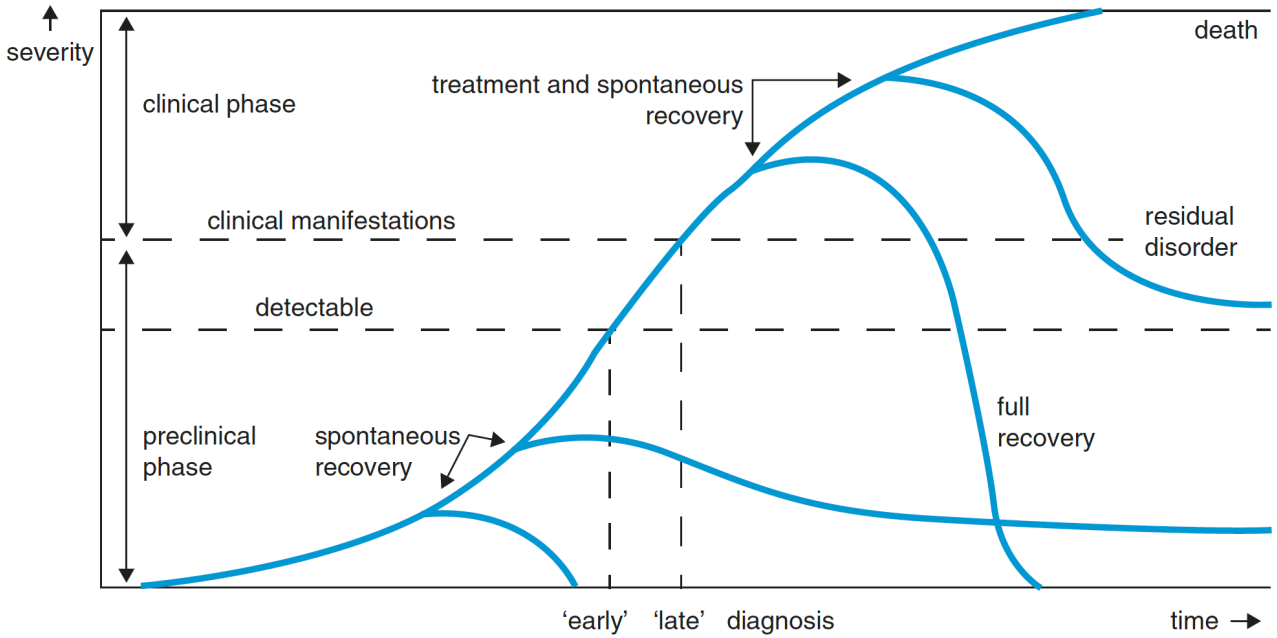
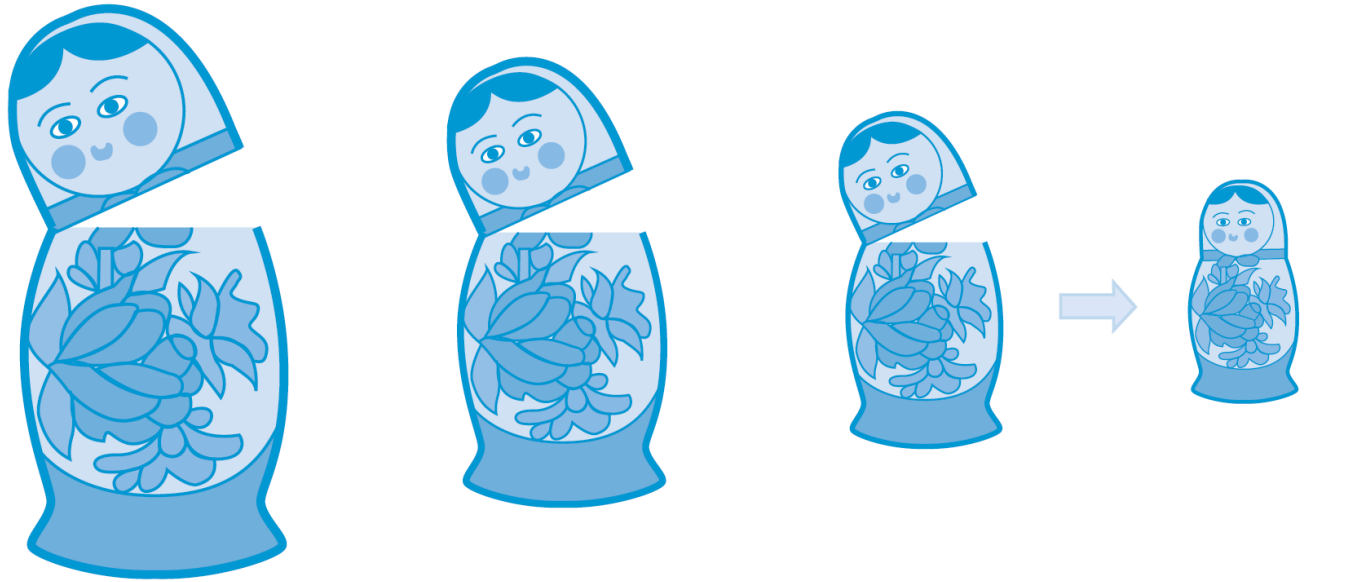
CAUSALITY (IMPORTANCE OF OUTCOMES)

1. Associations differ by outcome investigated (AML, genotoxic, haematotoxic)
2. Associations are different depending on disease stage being investigated



CAUSALITY (EXTERNAL VALIDATION)



PITFALLS

1. Causal Pathways
2. Safety Analyses
3. False Positives
4. Publication Bias
5. Robustness of Results (sensitivity analyses)
6. Indirectness of Evidence
7. Imprecision
8. Good Reporting is not good quality
9. Garbage in Garbage out

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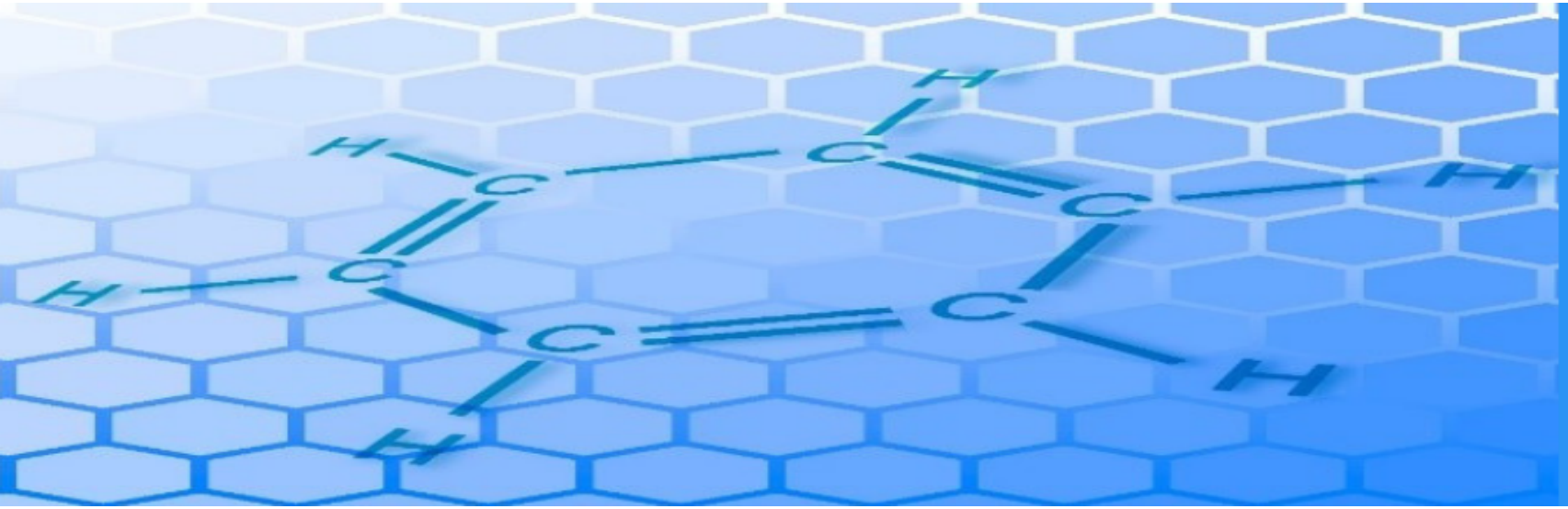
Aromatics Producers Association (APA)

Thank you … for your attention !

Quality assessment of
human observational studies of chemical exposure



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