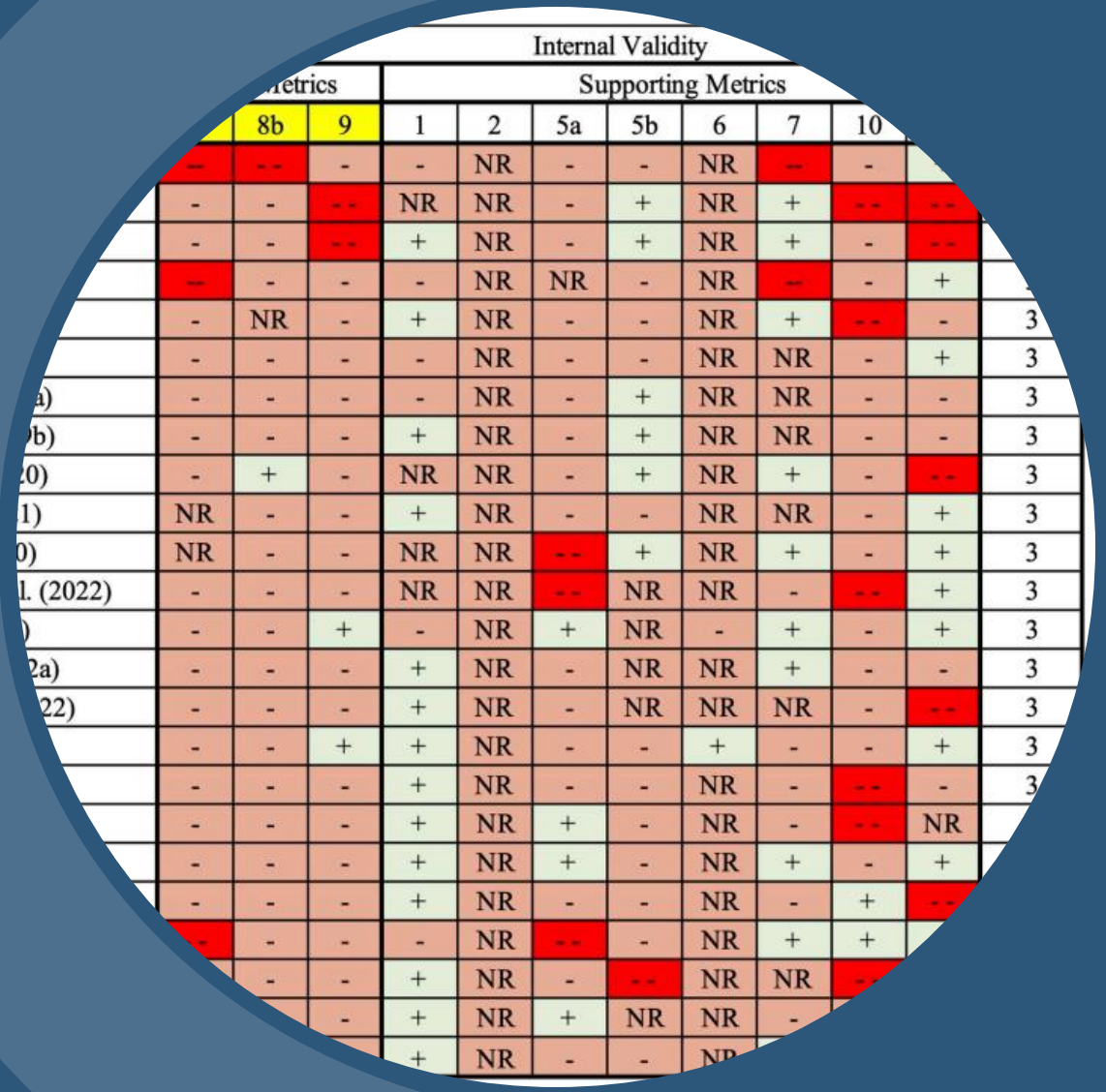


SYSTEMATIC REVIEW OF POTENTIAL DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF MICROPLASTICS

ROBERT ELLIS-HUTCHINGS

SENIOR TOXICOLOGIST - DOW

ACKNOWLEDGEMENTS

Seneca Fitch, John Rogers, Sue Marty, John Norman, Steffen Schneider, Erik Rushton, Daniele Wikoff

American Chemistry Council℠

PROJECTS OVERVIEW

Sampling Methods	Analytical Methods	Quality Control & Best Practices	Reference Materials	Ecotoxicity & Fate
• Sediment & Soil deposition • Indoor and Outdoor air	• Test Material characterization • Biological tissues	• Human Health Toxicity studies	• HPU Polymer Kit 1.0 & 2.0 • Expert workshop	• Threshold value determination

Additional

- AI assisted literature database
- Particle attributes: Lower size limit, Heteroaggregation

PLASTIC MICROPARTICLES STATE OF THE SCIENCE- HUMAN HEALTH

General consensus among scientific and regulatory agencies:

- Micro- and nanoplastics exposure has not been demonstrated to be a risk to human health.
- There are many limitations with the available data. More reliable data are needed.

World Health Organization

2019 & 2022

"The weight of the scientific evidence provided by current data on adverse effects of NMP on human health is low, because of substantial limitations of the available information."

FDA

2024

"Current scientific evidence does not demonstrate that levels of microplastics or nanoplastics detected in foods pose a risk to human health."

BfR

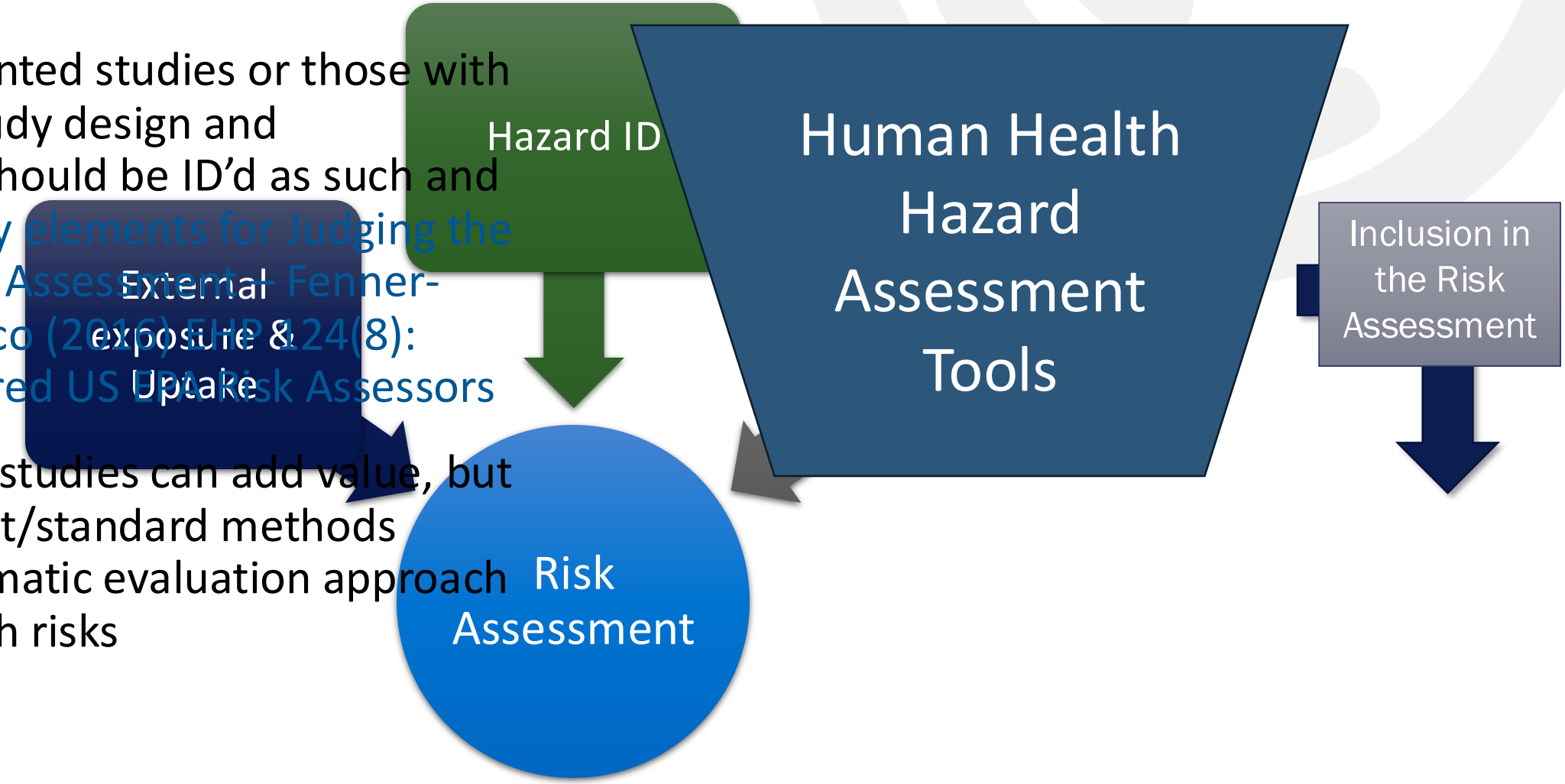
German Federal Institute for Risk Assessment

2025

"There is no reliable toxicological evidence of health risks from the ingestion of microplastics in food."

ACCELERATION OF MICROPLASTICS HUMAN HEALTH HAZARD AND RISK CONCLUSIONS - ASSESSMENT TOOLS

- "Poorly documented studies or those with questionable study design and reproducibility should be ID'd as such and not be used" Key elements for Judging the Quality of a Risk Assessment – Fenner-Crisp and Dellarco (2016) EHP 124(8): 1127-1135. Retired US EPA Risk Assessors
- Vast majority of studies can add value, but lack of consistent/standard methods requires a systematic evaluation approach for human health risks



ASSESSMENT TOOLS FOR HUMAN HEALTH RISK EVALUATION – TIER BASED SYSTEMATIC REVIEWS

Defining/Refining Criteria & Searching in Bibliographic Database

Specific Hypothesis

Inclusion or Exclusion based on Relevance

Assessing Reliability of Relevant Studies

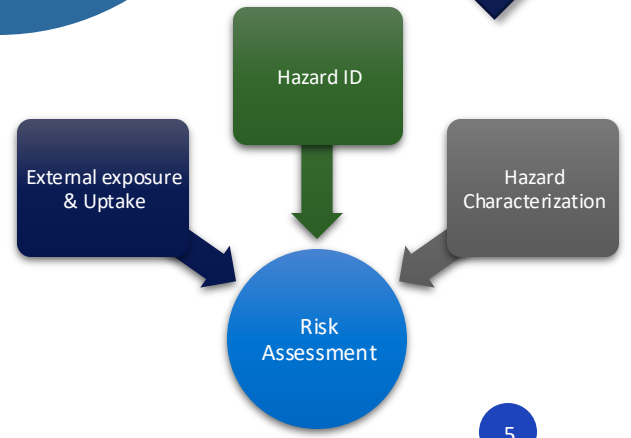
Tier 1 Screen

Tier 2 Expert Evaluation

Individual Studies + Overall Weight of Evidence

Extent to which the hypotheses are/are not supported

Inclusion in the Risk Assessment



EFSA

Adapted from Kaltenhäuser et al., 2017: EFSA Systematic Review for Peer-Reviewed Open Literature

NMP TOXICITY SCREENING ASSESSMENT TOOL – A TIER 1 APPROACH FOR HUMAN HEALTH HAZARD STUDIES


RESEARCH ARTICLE Open Access

Screening and prioritization of nano- and microplastic particle toxicity studies for evaluating human health risks – development and application of a toxicity study assessment tool

Todd Gouin[1*], Robert Ellis-Hutchings[2], Leah M. Thornton Hampton[3], Christine L. Lemieux[4] and Stephanie L. Wright[5]

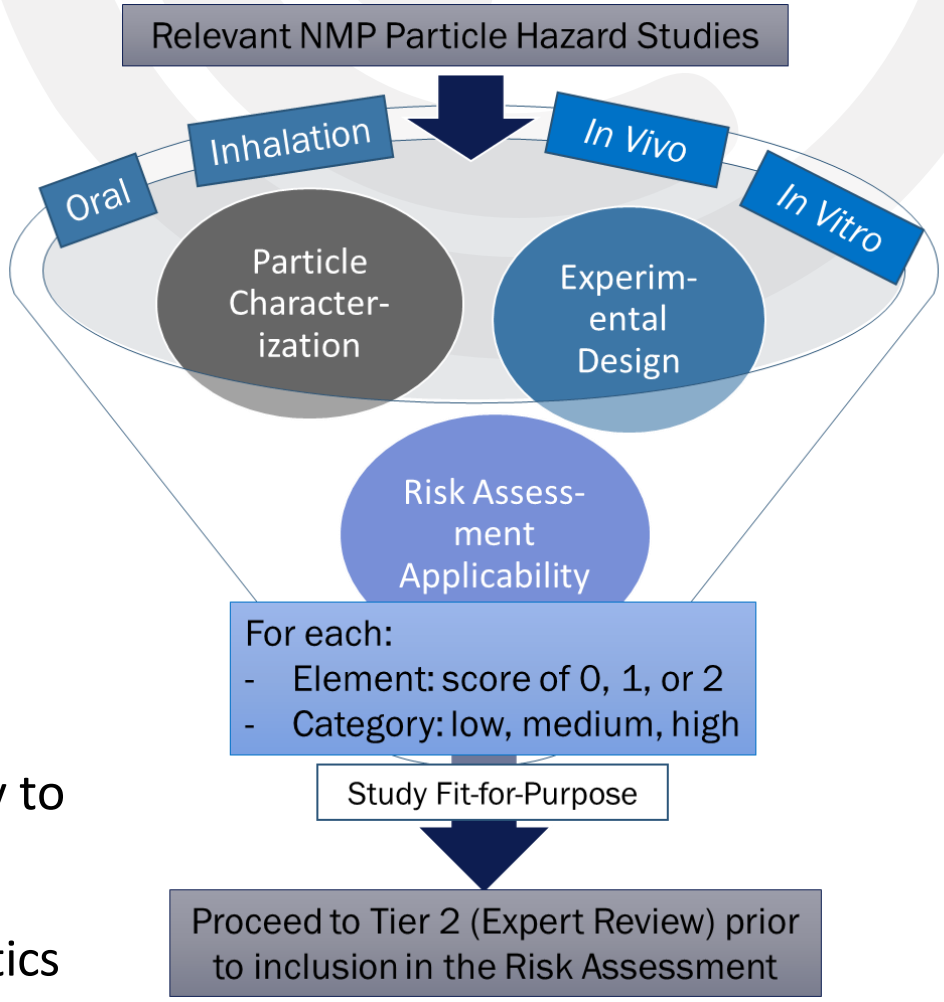
Check for updates

Aims

- Transparent, easily understood (qualitative & quantitative)
- Relevance & reliability
- Criteria: Particle Characteristics, Experimental design, Applicability to risk assessment

Combines elements of the Human health ToxRTool & the Microplastics Aquatic Biota screening criteria of de Ruitjer et al. (2020)

NMP Toxicity Study Assessment Tool



NEW APPROACH DEVELOPMENT – SYSTEMATIC REVIEW FOR MICRO/NANOPLASTICS (INCLUDING TIER 2)

Systematic review of potential developmental and reproductive toxicity of microplastics

Seneca Fitch [1,*], John Rogers [1], Sue Marty [2], John Norman [3], Steffen Schneider [4], Erik Rushton [5], Daniele Wikoff [1], Robert Ellis-Hutchings [2]

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[2]Dow, Midland, MI 48674, United States
[3]American Chemistry Council, Washington, DC 20002, United States
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Toxicological Sciences, 2025, **207(2)**, 289–305
https://doi.org/10.1093/toxsci/kfaf108

Key aspects

- New approach: Combines elements of NMP-TSAT and OHAT Risk of Bias
- Systematic Review – Evidence-based methods used by authoritative bodies (E.g. EPA, NTP)
- Includes Tier 2 expert review with refinements of critical appraisal approaches
  - Internal validity and Construct validity of each relevant study
- Focuses on an area of disproportionate research: Developmental and Reproductive Toxicity studies

OHAT RISK OF BIAS (ROB) TOOL

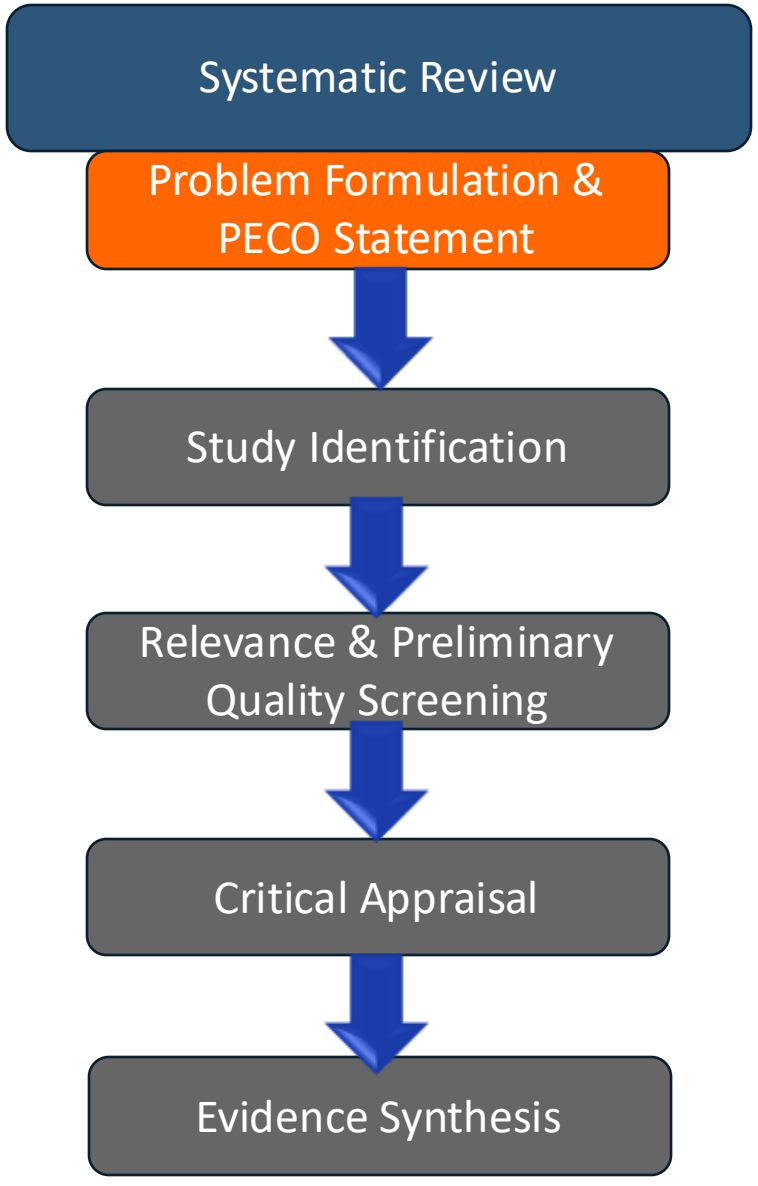
- OHAT RoB Tool developed by the US National Toxicology Program (NTP) within the National Institute of Environmental Health Sciences (NIEHS-NIH)
- Has the credibility of the link between exposure outcome been compromised by the study design and conduct?
- Bias is a systematic error, or deviation from the truth, in results or inferences
  - Can lead to under- or overestimation of true effect
- **Risk-of-bias domains for observational studies**
- **Four risk-of-bias response options for each domain:**

Definitely Low	Probably Low	Probably High	Definitely High
Direct evidence of low RoB practices	Indirect evidence of low RoB practices	Indirect evidence of high RoB practices	Direct evidence of high RoB practices

- RoB assessed for: Individual studies & across studies

- 6 Domains (types of bias)
- 11 questions
  - NMP-TSAT + OHAT
  - Danopoulos et al. (2022)

SYSTEMATIC REVIEW

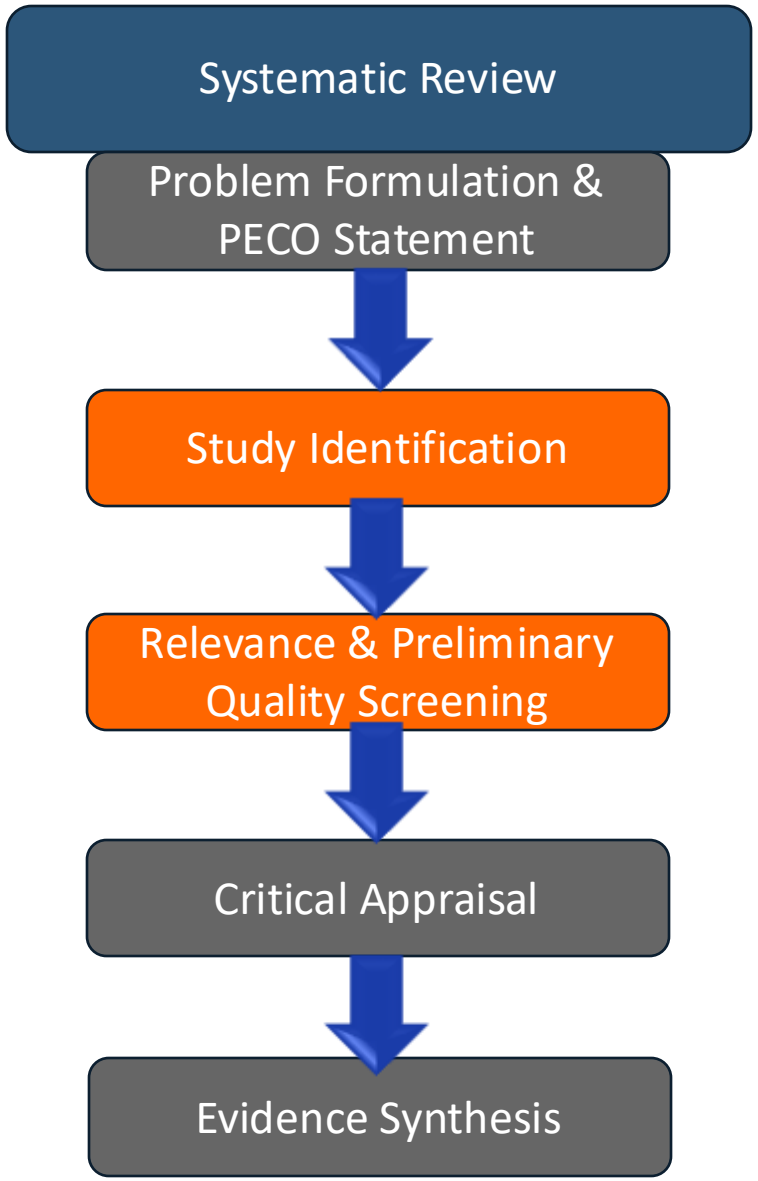


Problem Formulation

What is the hazard and dose-response relationship between exposure to MPs and reproductive and developmental adverse effects in mammals?

PECO Element	Inclusion Criteria	Exclusion Criteria (selected)
Population	Human	Non-mammalian models
	Animal	In vitro, ex vivo, in silico
Exposure	Exposures to microplastics (Definition: Plastic particles 0.1 µm to 5 mm)	Doses/concentrations not reported[a]
	Oral, inhalation, or dermal routes of any exposure duration and frequency	Duration/frequency of exposure not reported[a]
	≥ 2 treatment groups OR multiple particle characteristics (e.g. sizes)[a]	Particle size or Polymer type not reported[a]
		Polymer type not reported[a]
Comparator	Include untreated or vehicle negative control	No appropriate comparator
		Negative or concurrent control not reported
Outcome	Outcomes related to mammalian male and female DART endpoints	Outcomes unrelated to DART endpoints

SYSTEMATIC REVIEW



Search dates (# unique references)
12/2021 (n=1901)
9/2022 (n=275)
4/2023 (n=229)
9/2023 (n=219)

TiAb Screening
n = 2625

Exclude (n=2564)

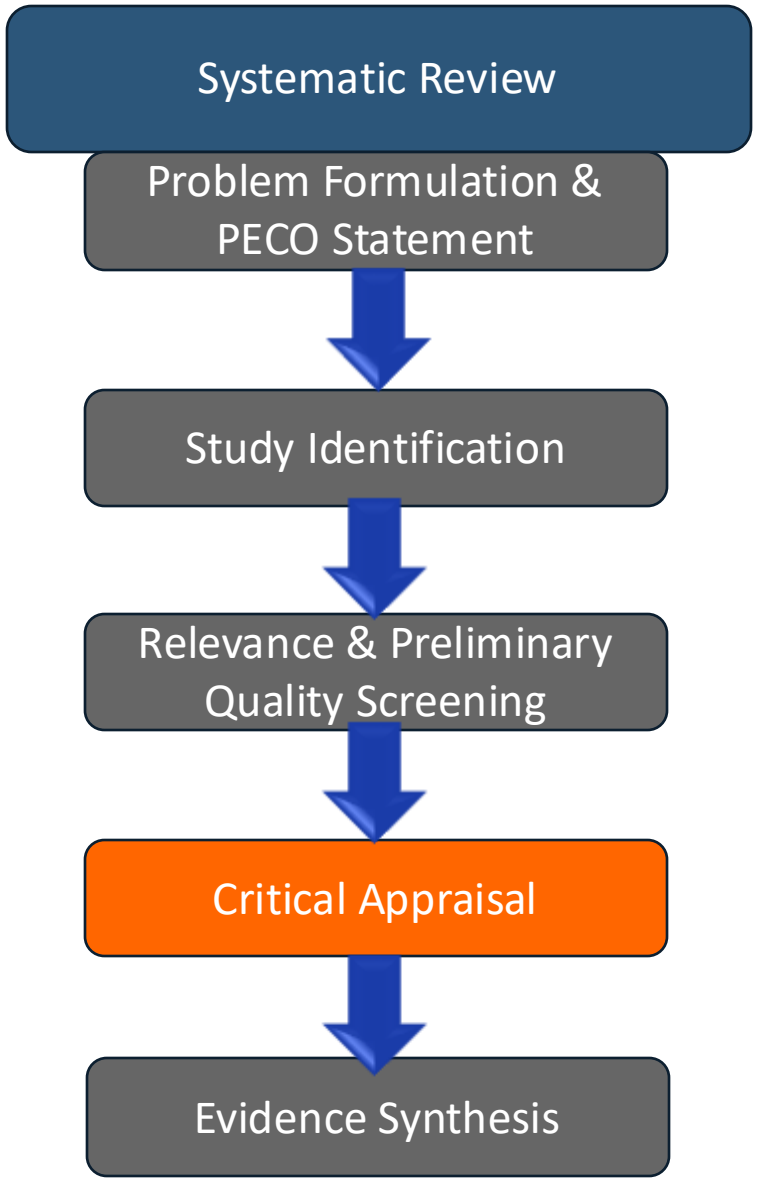
Full-text screening
n = 60

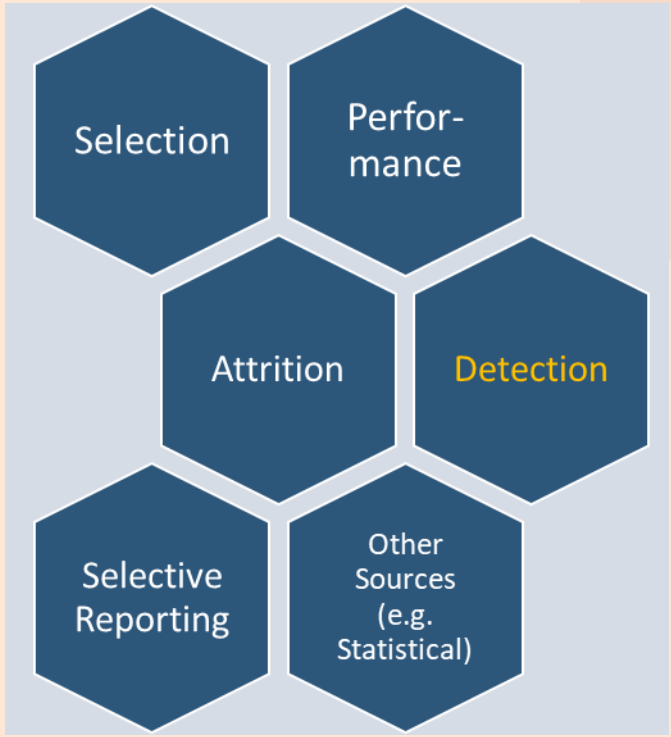
Exclude (n=36)

Individual study assessment
n =24

Summary of exclusion reasons at full-text
< 2 NMP groups (n=16)
Particle size (n=13)
Inadequate reporting (n=2)
Irrelevant route (n=2)
No DART outcomes (n=1)
Tier 1 quality criteria not met (n=2)

SYSTEMATIC REVIEW – CRITICAL APPRAISAL (24 STUDIES)





Definitely Low
Direct evidence of low RoB practices

Probably High
Indirect evidence of high RoB practices

Probably Low
Indirect evidence of low RoB practices

Definitely High
Direct evidence of high RoB practices

Key Domain - Detection

8a. Can we be confident in the **exposure** characterization? (**test agent/particle characterization**)

8b. Can we be confident in the **exposure** characterization? (**test agent administration**)

9. Can we be confident in the **outcome** assessment?

Other Domains (9 Questions)

Selection - Randomization, Blinding
Performance – Experimental conditions (vehicle, feed, housing)
Attrition – Data exclusion
Selective Reporting
Other Sources – Statistical methods

Assessment Conclusion Categories

Internal Validity = Tier I, II, III
Construct Validity = High, Medium, Low, Unacceptable

SYSTEMATIC REVIEW – CRITICAL APPRAISAL RESULTS

Systematic Review

Problem Formulation & PECO Statement

Study Identification

Relevance & Preliminary Quality Screening

Critical Appraisal

Evidence Synthesis

Individual study assessment n =24

- 11 NMP + OHAT questions

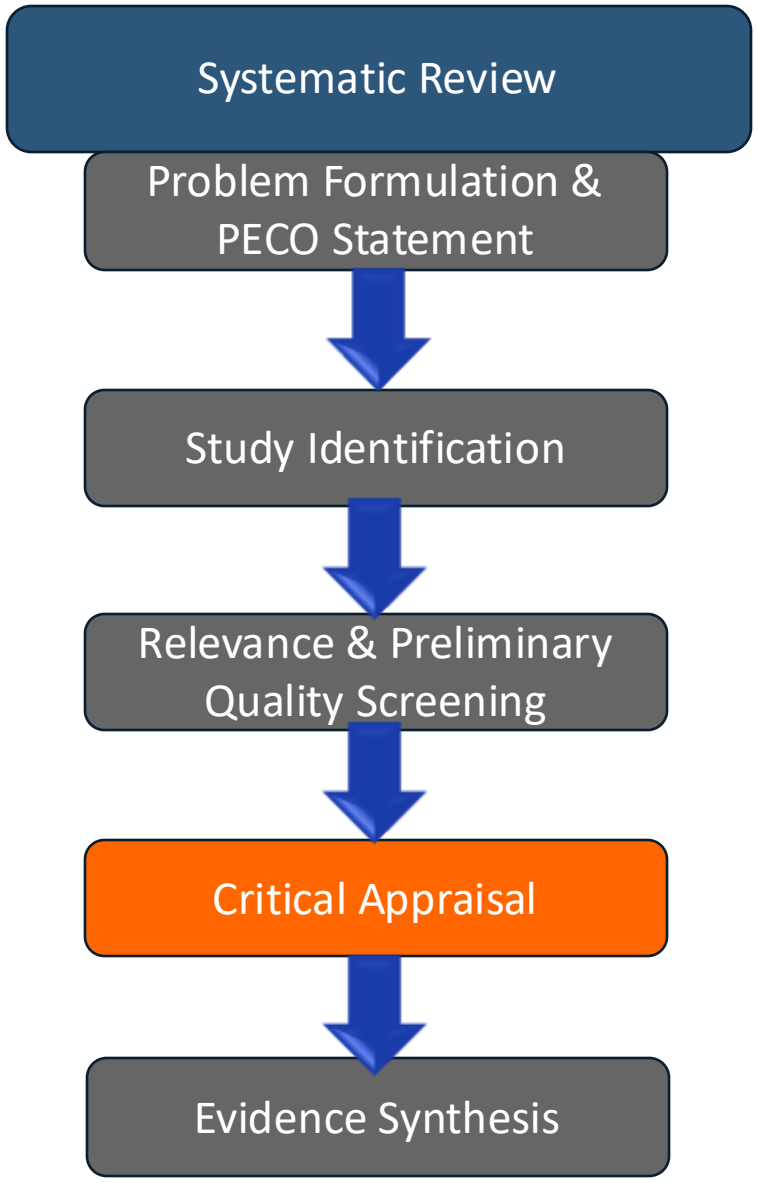
Definitely Low	Probably High
Direct evidence of low RoB practices	Indirect evidence of high RoB practices
Probably Low	**Definitely High**
Indirect evidence of low RoB practices	Direct evidence of high RoB practices

Tier III OR low, unaccep. n = 24

Tier 1 or II AND medium, high n = 0

Sufficient for risk assessment n = 0

SYSTEMATIC REVIEW – CRITICAL APPRAISAL RESULTS



	Internal Validity												Construct Validity
	Key Metrics			Supporting Metrics								Overall Tier	Characterization of the construct of a study relative to PECO
	8a	8b	9	1	2	5a	5b	6	7	10	11		
An et al. (2021)	--	- -	-	-	NR	-	-	NR	--	-	+	3	Medium
Han et al. (2021)	-	-	- -	NR	NR	-	+	NR	+	- -	- -	3	Unacceptable
Hou et al. (2021a)	-	-	- -	+	NR	-	+	NR	+	-	- -	3	Medium
Hou et al. (2021b)	--	-	-	-	NR	NR	-	NR	--	-	+	3	Medium
Jin et al. (2021a)	-	NR	-	+	NR	-	-	NR	+	- -	-	3	Medium
Li et al. (2021)	-	-	-	-	NR	-	-	NR	NR	-	+	3	Medium
Luo et al. (2019a)	-	-	-	-	NR	-	+	NR	NR	-	-	3	Medium
Luo et al. (2019b)	-	-	-	+	NR	-	+	NR	NR	-	-	3	Medium
Park et al. (2020)	-	+	-	NR	NR	-	+	NR	+	-	- -	3	Medium
Wei et al. (2021)	NR	-	-	+	NR	-	-	NR	NR	-	+	3	Low
Xie et al. (2020)	NR	-	-	NR	NR	- -	+	NR	+	-	+	3	Medium
Ilechukwu et al. (2022)	-	-	-	NR	NR	- -	NR	NR	-	- -	+	3	Medium
Jin et al. (2022)	-	-	+	-	NR	+	NR	-	+	-	+	3	Medium
Wen et al. (2022a)	-	-	-	+	NR	-	NR	NR	+	-	-	3	Medium
Aghaei et al. (2022)	-	-	-	+	NR	-	NR	NR	NR	-	- -	3	Low
Cui et al. (2023)	-	-	+	+	NR	-	-	+	-	-	+	3	Low
Zhang et al. (2023)	-	-	-	+	NR	-	-	NR	-	- -	-	3	Medium
Chen et al. (2022)	-	-	-	+	NR	+	-	NR	-	- -	NR	3	Low
Wen et al. (2023b)	-	-	-	+	NR	+	-	NR	+	-	+	3	Medium
Zhao et al. (2023)	-	-	-	+	NR	-	-	NR	-	+	- -	3	Medium
Saeed et al. (2023)	- -	-	-	-	NR	- -	-	NR	+	+	+	3	Medium
Lu et al. (2023)	-	-	-	+	NR	-	- -	NR	NR	- -	NR	3	Medium
Wu et al. (2023)	-	-	-	+	NR	+	NR	NR	-	-	+	3	Low
Ma et al. (2023)	-	-	-	+	NR	-	-	NR	+	- -	+	3	Medium

SYSTEMATIC REVIEW - CONCLUSIONS

- No study advanced to the evaluation of sufficiency for risk assessment
  - Inconsistent exposure characterization, poor outcome assessment, lack of adherence to validated guidelines
- All studies considered unreliable in terms of understanding the true effect of an exposure.
  - Regulatory context: Klimisch 3 (Not Reliable) or 4 (Not Assignable)
  - Regulatory use: Often excluded or given minimal weight in decision-making
- Characterizing the reproductive and developmental toxicity of MPs based on this body of evidence is not advised

Not all systematic reviews are equivalent (E.g. Chartres et al., 2024)

Navigation Guide methodology differs from the OHAT RoB in 2 significant ways:

1) Does not include Exposure parameter in critical evaluation.

2) Assumes experimental animal data are of “high” quality equivalent to human randomized control trials.

FEATURES NEEDED TO INCREASE CONFIDENCE IN RELIABILITY AND REDUCED BIAS

- Utilize environmentally relevant test materials and document their justification.
- Fully characterize the test materials, including particle surface features and non-particle components.
- Analytical Dose Confirmation is needed: dose stability, suspension/homogeneity, and concentration in the test system covering the duration of the administration.
- Methods are sufficiently detailed so that study replication is possible.
- For reproductive endpoints (functional, hormonal, structural), a detailed assessment of the general health of the parental unit is available for comparison.
- Assessment methods for effects endpoints are valid, reliable, and sufficiently robust to be consistent with the principles of the relevant regulatory test guidelines.

OVERALL CONCLUSIONS

- Scientific and regulatory agency general consensus: Insufficient evidence to assess potential risks of plastic NMP to human health
- Assessment tools will help to accelerate derivation of human health risk conclusions for micro/nanoplastics
- Using systematic review principles, a fit-for-purpose tier 1 (screening) and tier 2 (expert review) approach was developed (incorporated NMP-TSAT and OHAT Risk of Bias tools)
- For developmental and reproductive toxicity studies, no study was sufficiently reliable to be sufficient for evaluation in a risk assessment
  - Inconsistent exposure characterization, poor outcome assessment, lack of adherence to validated guidelines
- Increased confidence in reliability and reduced bias is achievable by employing key features.

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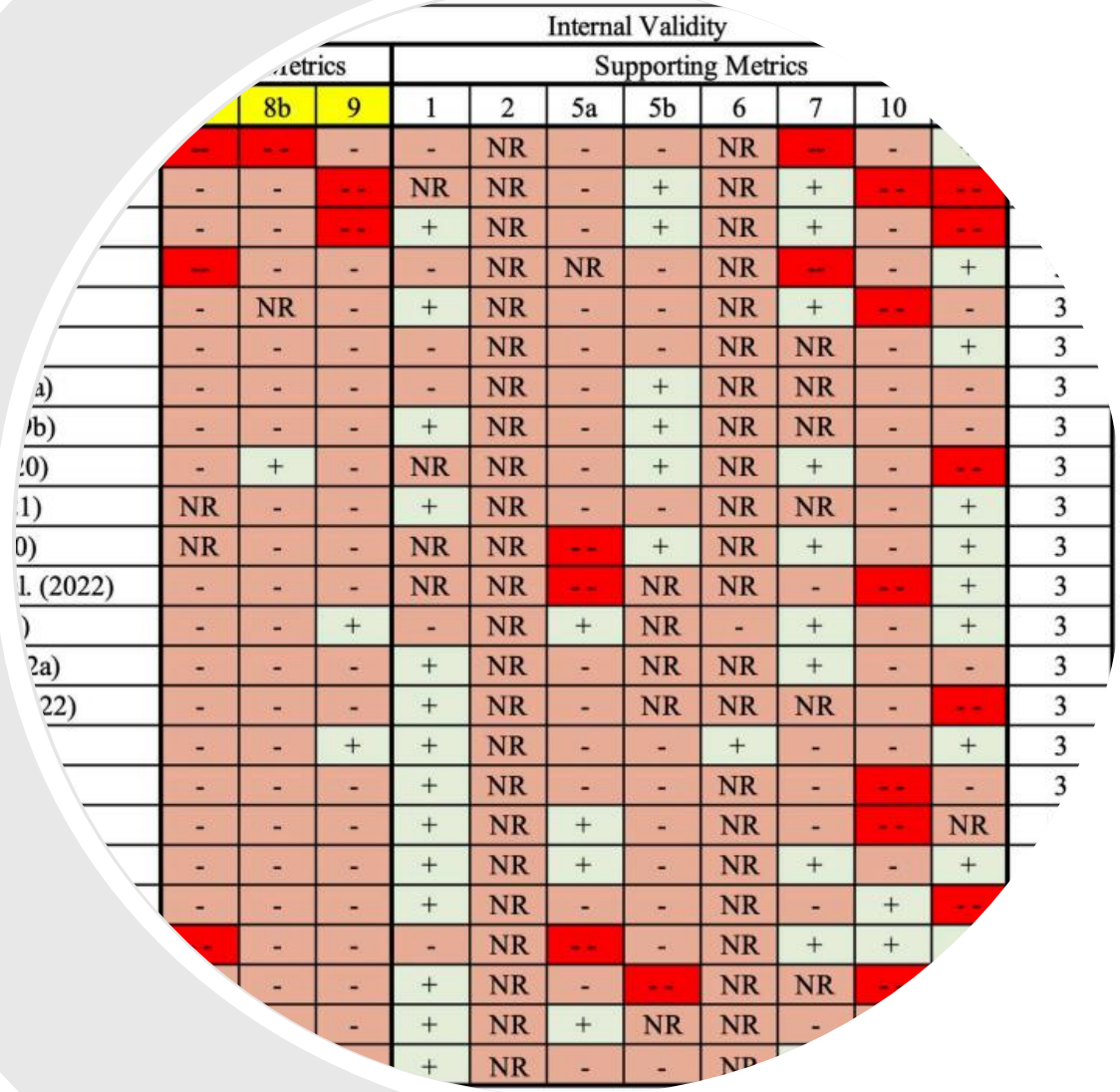

THANK YOU

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