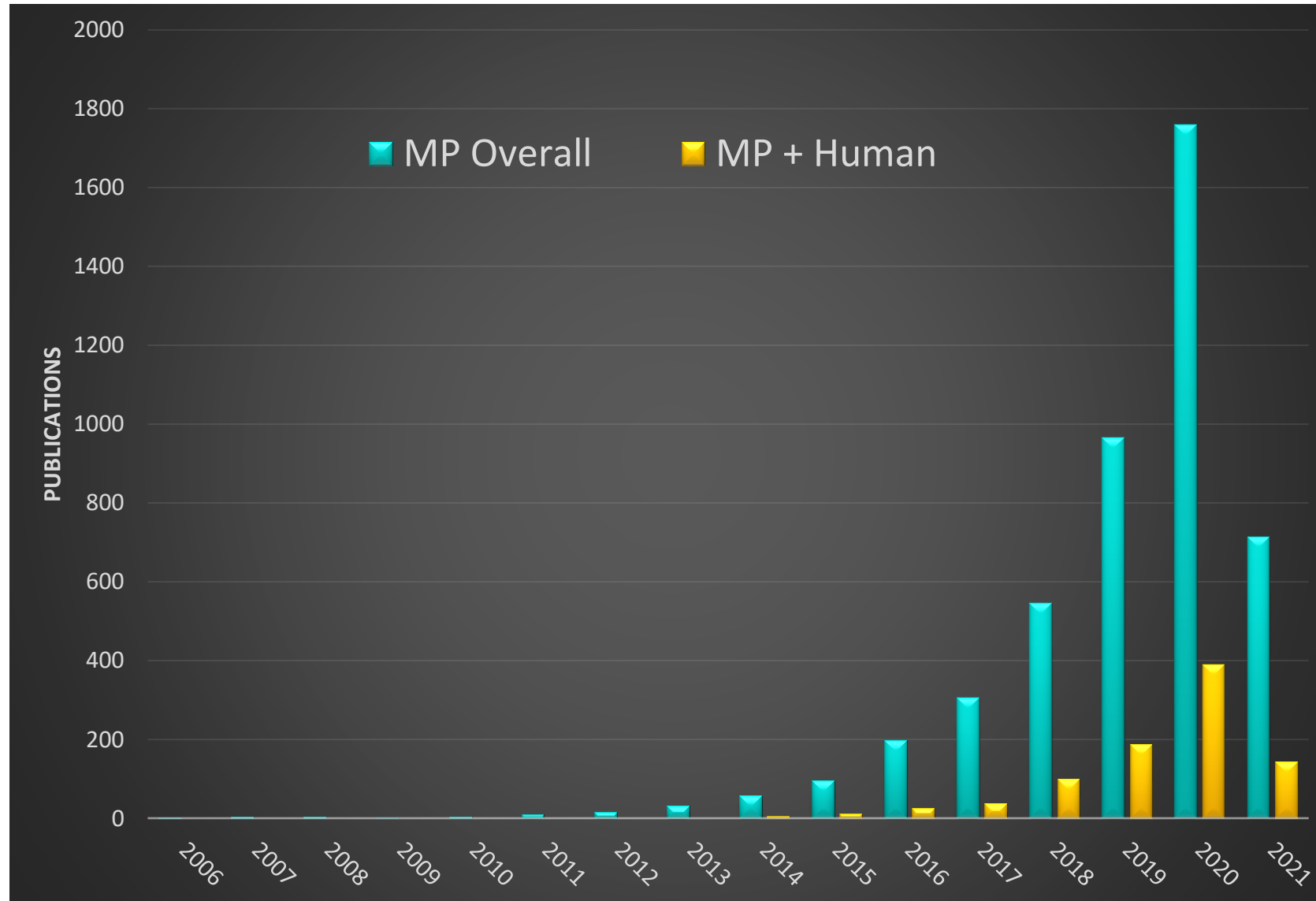


**SCREENING &  
PRIORITIZATION OF  
NANO- AND MICROPLASTIC  
PARTICLE TOXICITY  
STUDIES FOR EVALUATING  
HUMAN HEALTH RISKS**

**Rob Ellis-Hutchings, Ph.D., DABT**  
**Toxicologist - Dow, Inc.**



# PROLIFERATION OF MICROPLASTICS SCIENCE



# MICROPLASTICS - HUMAN HEALTH ASSESSMENTS

**STATEMENT**

**EFSA - 2016**



ADOPTED: 11 May 2016  
doi: 10.2903/j.efsa.2016.4501

**Presence of microplastics and nanoplastics in food, with particular focus on seafood**

EFSA Panel on Contaminants in the Food Chain (CONTAM)

[www.bfr.bund.de](http://www.bfr.bund.de)

**BfR - 2018**



Bundesinstitut für Risikobewertung

Is there a risk to human health from microplastics? More research and scientific data needed

BfR Communication No 033/2018 of 29.10.2018

**Micro- and nanoplastics – current state of knowledge with the focus on oral uptake and toxicity**


Maxi B. Paul,<sup>a</sup> Valerie Stock,<sup>a</sup> Julia Cara-Carmona,<sup>a</sup> Elisa Lisicki,<sup>a</sup> Sofiya Shopova,<sup>a</sup> Valérie Fessard,<sup>b</sup> Albert Braeuning,<sup>a</sup> Holger Sieg<sup>ib\*</sup> and Linda Böhmert<sup>a</sup>

**BfR & ANSES - 2021**

**WHO - 2019**


Studies quality scored

**Microplastics in drinking-water**



World Health Organization

**Science assessment of plastic pollution**



Environment and Climate Change Canada

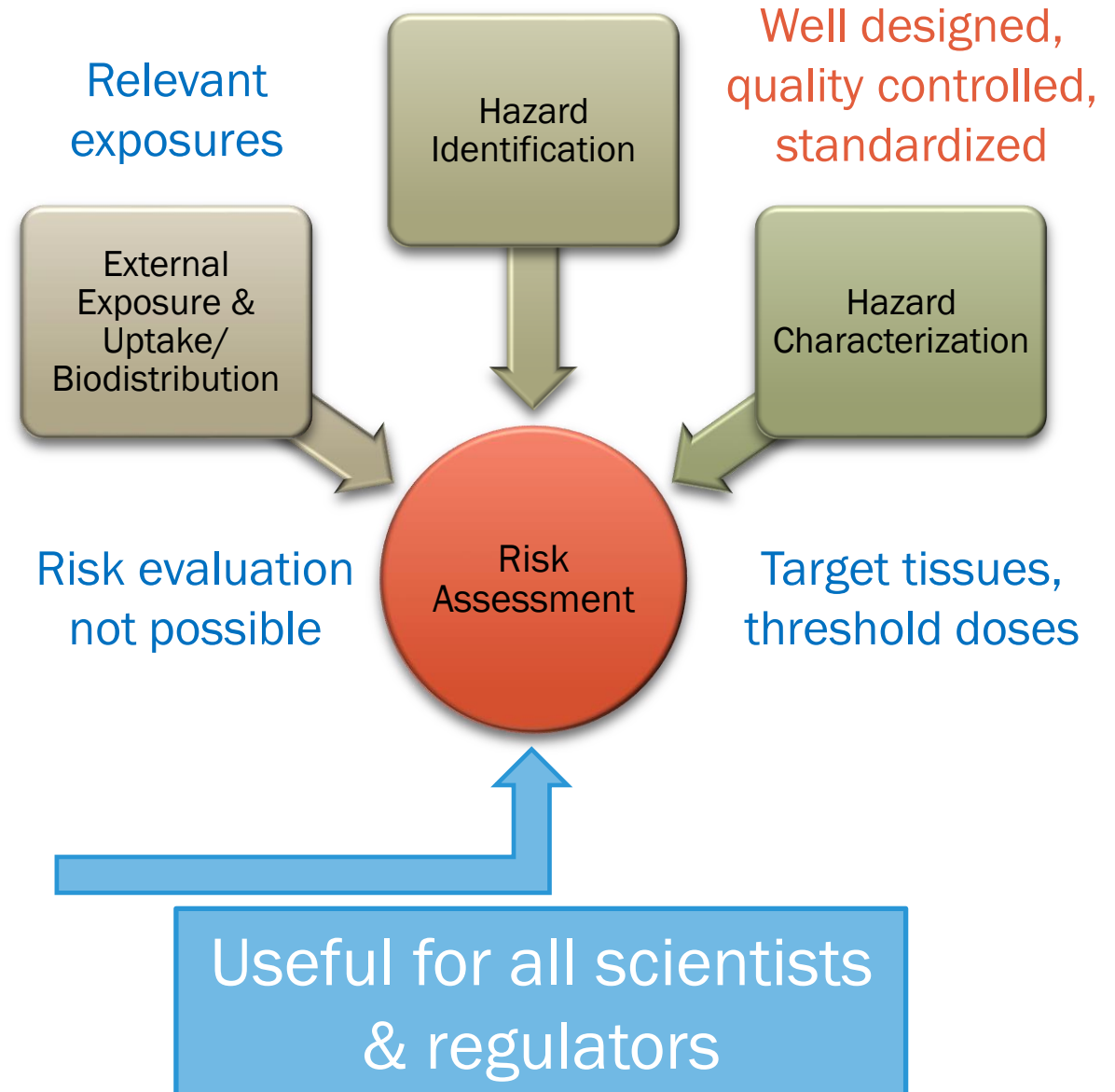
Health Canada

October 2020

**ECCC - 2020**

# CONCLUSIONS FROM AUTHORITY ASSESSMENTS

We Need More Data

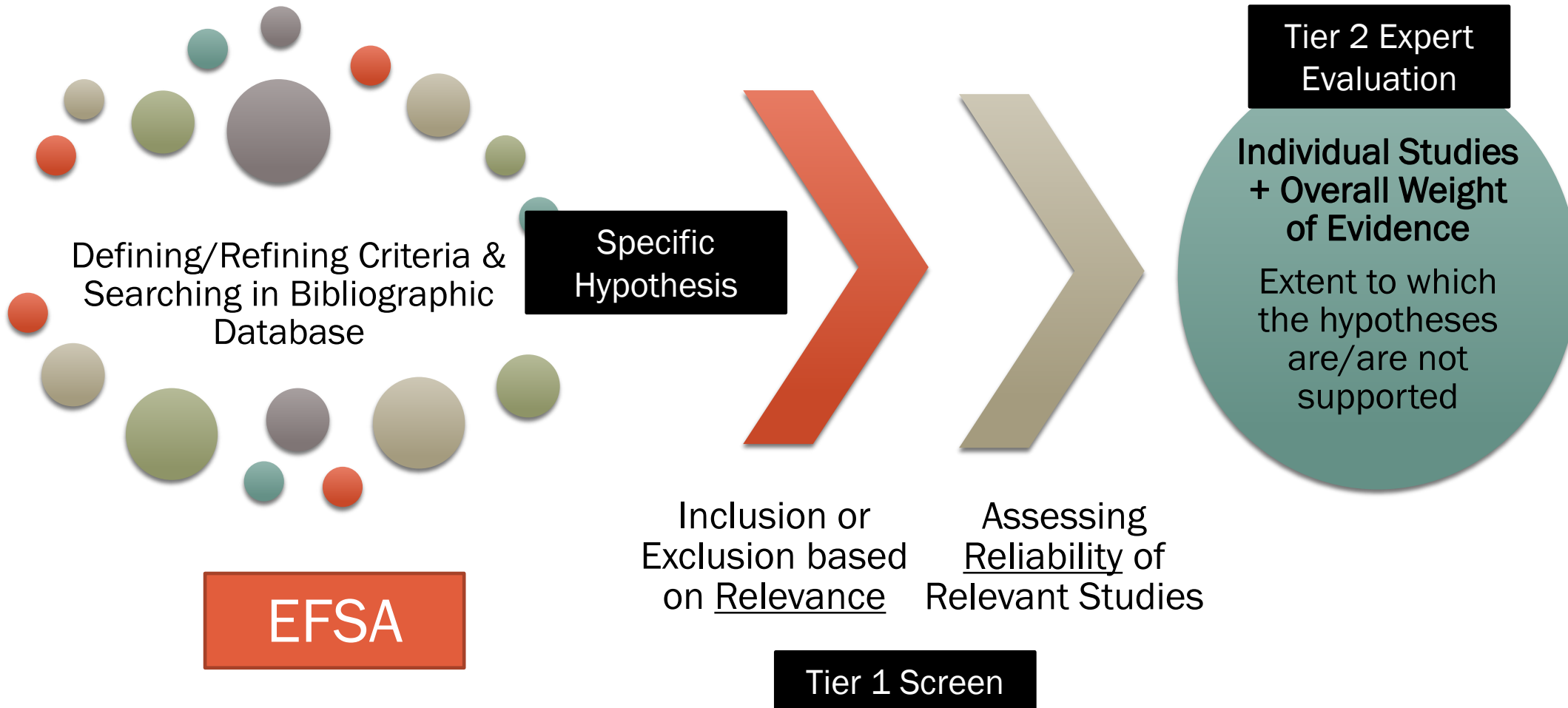


# LACK OF CONSISTENT AND STANDARD METHODS – TIER BASED SYSTEMATIC REVIEWS NEEDED FOR HUMAN HEALTH RISK EVALUATIONS

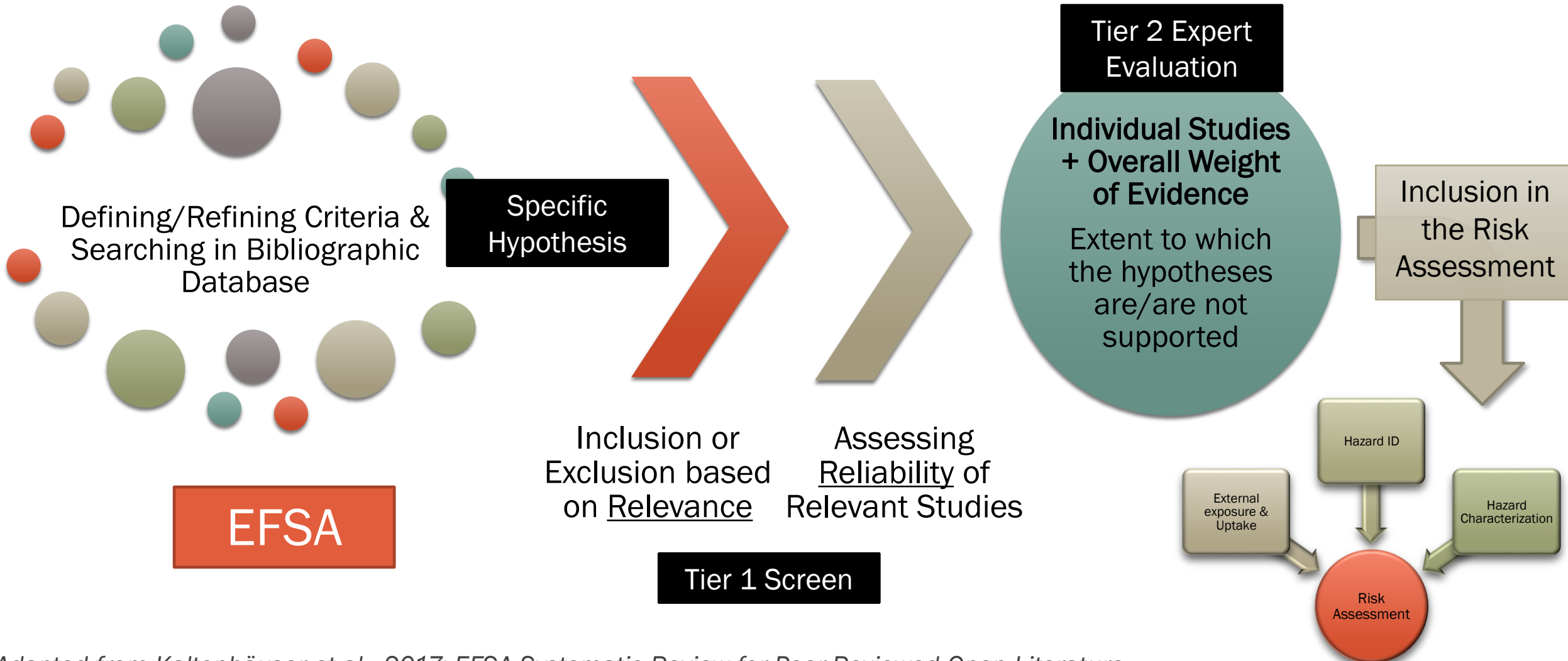


# LACK OF CONSISTENT AND STANDARD METHODS - TIER BASED

## SYSTEMATIC REVIEWS NEEDED FOR HUMAN HEALTH RISK EVALUATIONS



# LACK OF CONSISTENT AND STANDARD METHODS - TIER BASED SYSTEMATIC REVIEWS NEEDED FOR HUMAN HEALTH RISK EVALUATIONS





# STANDARDIZATION OF DATA QUALITY & ASSESSMENT CRITERIA – HUMAN HEALTH TIER 1 SCREENING

- Efforts to date largely focused on regulatory test guideline studies

➤ Klimisch reliability code (*Klimisch et al., 1997*)

- ✓ Qualitative
- ✓ Adequacy, Relevance, Reliability
- ✓ Reliable (1 = without, 2 = with restrictions),  
3 = Not reliable, 4 = Not assignable



➤ ToxRTool - Toxicological data Reliability Assessment Tool (*Scheider et al., 2009*) **21 Criteria**

- ✓ EURL ECVAM (EC JRC); Qualitative & quantitative elements, *in vivo* and *in vitro* ↑ Transparency
- ✓ US EPA evaluated for regulatory hazard assessments (*Segal et al., 2015*) Useful in initial review steps

➤ GUIDEnano – ToxRTool adapted for nanomaterials (*Fernandez-Cruz et al., 2018*) Ecotox + Human health  
**29-32 Criteria**



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**29-32 Criteria**

- Microplastics & Human health - No study quality or assessment criteria

# DEVELOPMENT OF A **NANO/MICROPLASTIC** SCREENING APPROACH – **HUMAN HEALTH HAZARD STUDIES TIER 1**

- “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

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- Vast majority of studies can add value, but lack of consistent/standard methods requires a systematic evaluation approach for human health risks

- Aim: Develop a Tier 1 evaluation tool to screen *in vivo* mammalian and *in vitro* NMP hazard studies for use in human health risk assessments
  - ✓ Transparent, easily understood (qualitative & quantitative)
  - ✓ Relevance, reliability of study results
  - ✓ Criteria: Particle characteristics, Experimental design, Applicability to risk assessment
- Combines elements of the ToxRTool + de Ruitjer et al. (2020) screening criteria



# NANO/MICROPLASTIC PARTICLE TOXICITY STUDY ASSESSMENT TOOL (NMP-TSAT)

## Particle Characterization

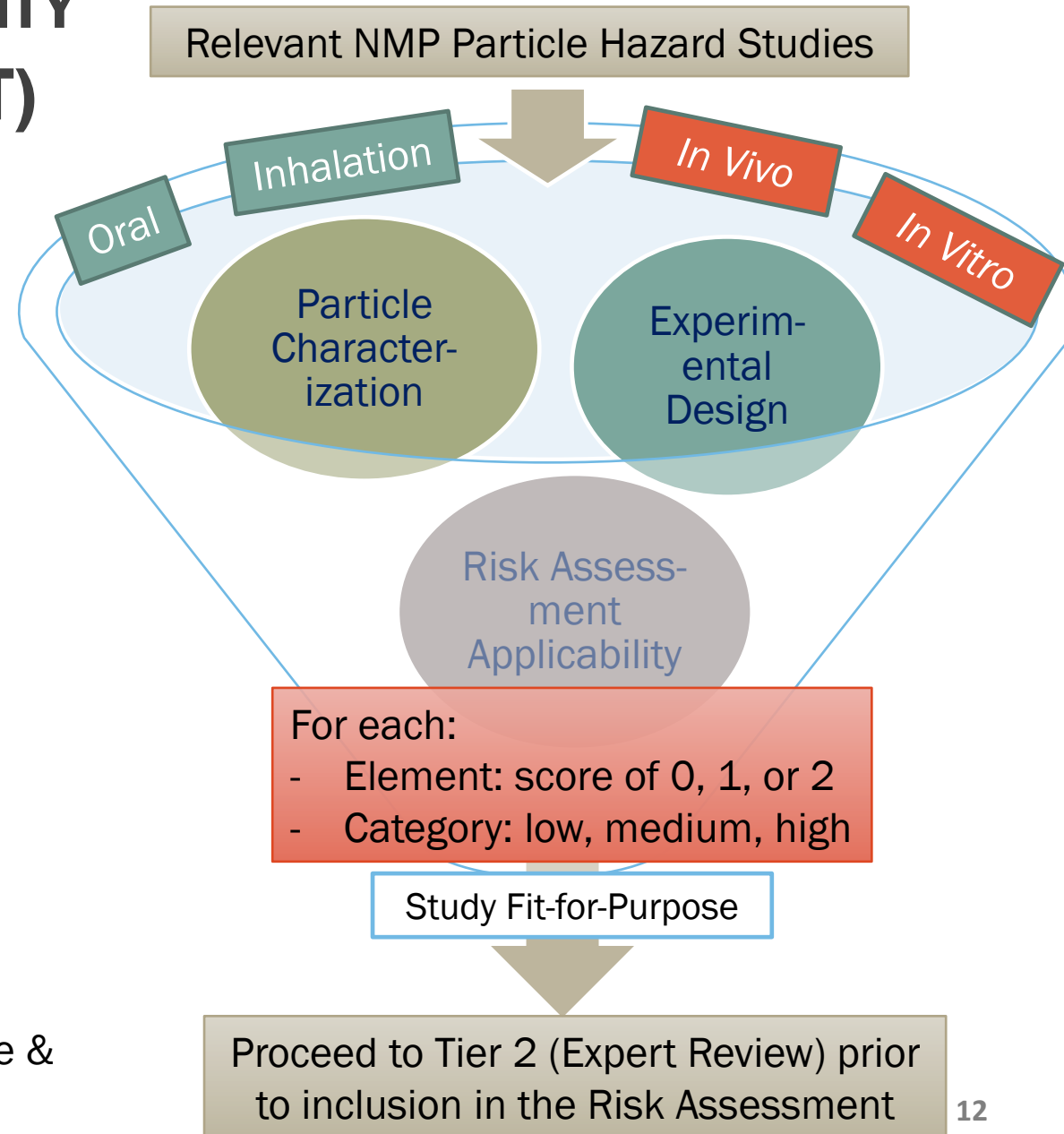
- 1) Size
- 2) Shape
- 3) Type
- 4) Source
- 5) Surface Chemistry
- 6) Purity
- 7) Microbial Contamination

## Applicability for Risk Assessment

- 1) Statistical Analysis
- 2) Endpoints
- 3) Dose-response Relationship
- 4) Concentration Range
- 5) Effect Thresholds
- 6) Test Particle Relevance

## Experimental Design

- 1) Particle Concentration Units
- 2) Particle Stability
- 3) Test Medium/Vehicle
- 4) Administered Dose/Concentration
- 5) Homogeneity of Exposure
- 6) Administration Route
- 7) Test Species
- 8) Feeding/Housing Conditions
- 9) Sample Size
- 10) Frequency & Duration of Exposure
- 11) Controls (Vehicle and/or Particle)
- 12) Replicates
- 13) Confirmation of internal dose



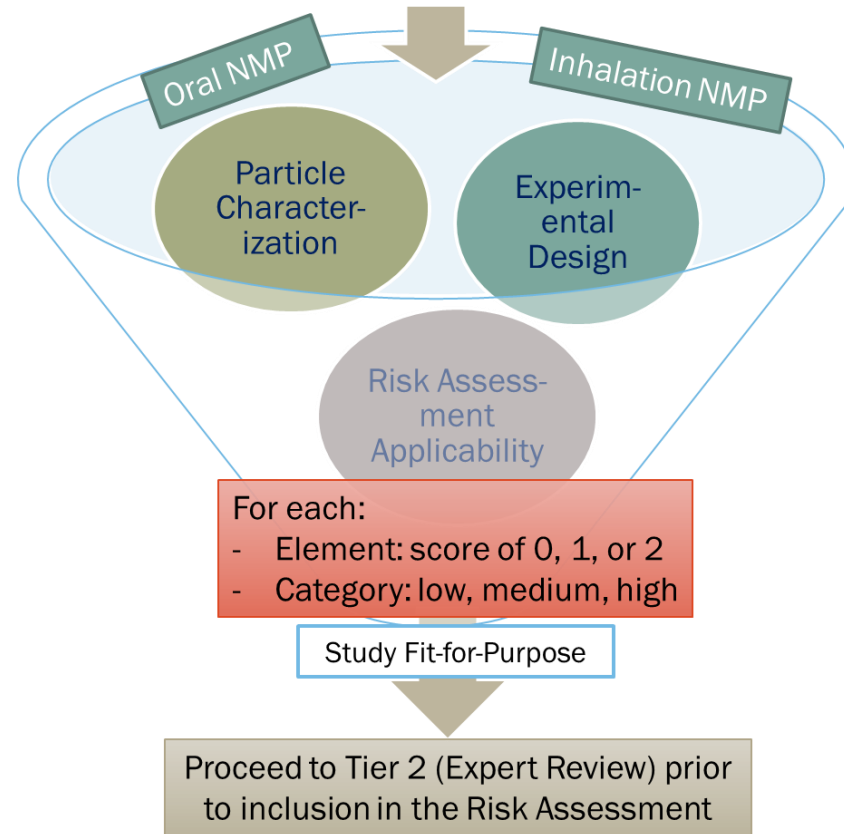
**Red criteria = Critical.** If scored as 0, then study = unreliable & concluded not fit-for-purpose for use in a risk assessment.

# NMP-TSAT: *In Vivo* Studies Assessed

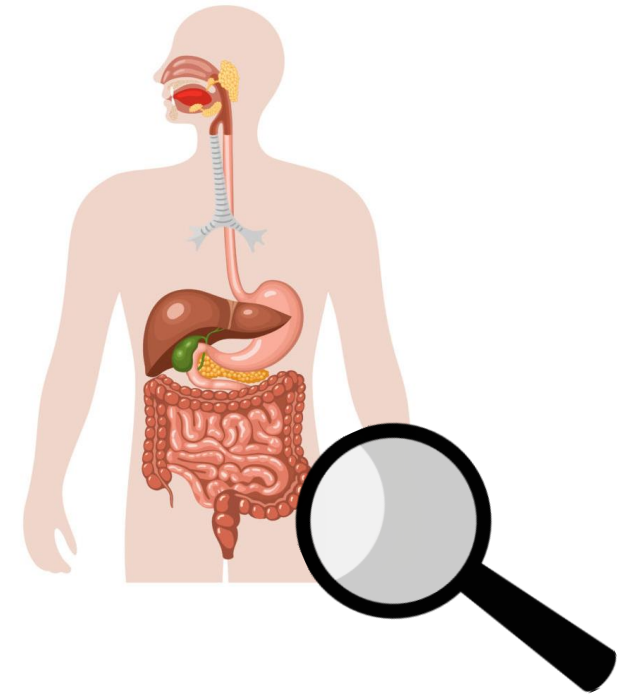
**Inhalation**  
**16 studies**  
**- 1 OECD guideline**



40 NMP + cellulose comparison studies



**Oral**  
**24 studies**  
**- 2 OECD guideline**



# NMP TOXICITY STUDY ASSESSMENT TOOL (TIER 1) – LEARNINGS ABOUT NMP STATE OF THE SCIENCE

## Strengths/Sufficient Reporting

Studies mostly used biologically- relevant sizes  
(0.01 – 200 micron)

Particle characteristics sufficiently reported  
Size, shape, type, source

Experimental design sufficiently reported  
Particle concentration, test vehicle, route,  
species/bioassay details, sample size, replicates,  
controls, frequency/duration

Applicability to risk assessment sufficiently reported  
Statistical analysis, description of endpoints



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Applicability to risk assessment sufficiently reported  
Statistical analysis, description of endpoints

## Needed Improvements

**Limited particle diversity:** majority using spheres (~60%), primarily of polystyrene (~46%); fibers (~20%)

**Limited particle sources** (45% from five suppliers)

**Particles not fit-for-purpose**

Equipment calibration, protein ligand substrate

**Test material purity unknowns:** particle, unreacted monomers, surfactants/dispersants, vehicle (e.g. Ethanol)

Particle characteristics insufficiently reported

Particle surface chemistry, microbial contamination

Experimental design insufficiently reported

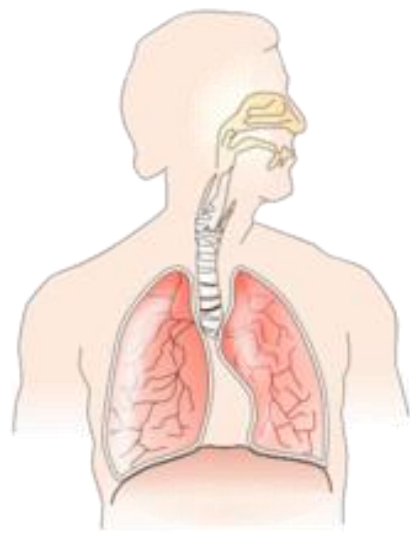
Particle stability, homogeneity, internal dose confirmation

Applicability to risk assessment insufficiently reported

Environmental relevance of particle tested or exposure scenario, <2 test concentrations (~50%), not possible to evaluate D-R relationship or determine effect thresholds.

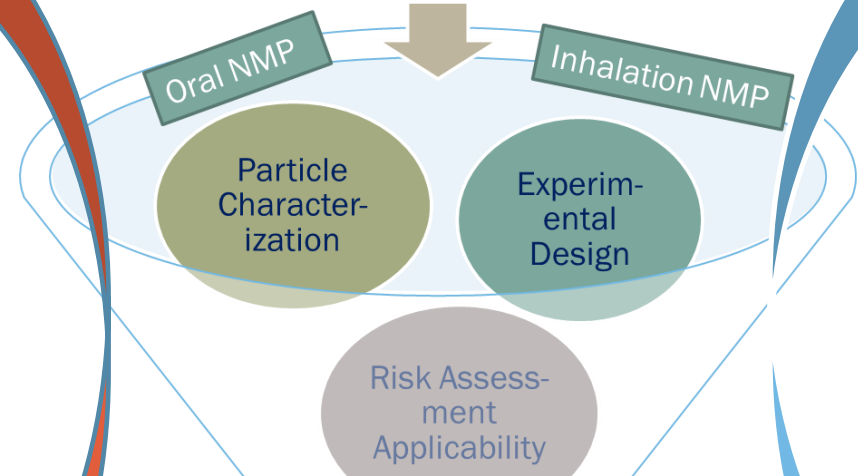
# NMP-TSAT: *In Vivo* Studies Assessed VS. RELIABLE TO PROCEED TO TIER 2

**Inhalation**  
**16 studies**  
**- 1 OECD guideline**



**2 studies**

40 NMP + cellulose comparison studies

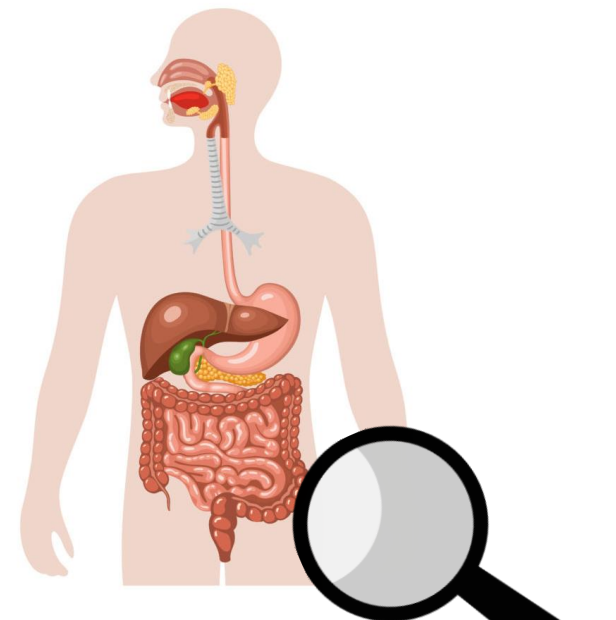


For each:  
- Element: score of 0, 1, or 2  
- Category: low, medium, high

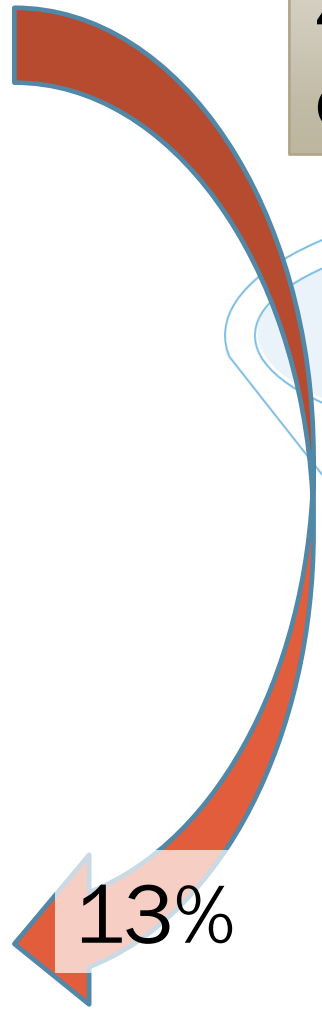
Study Fit-for-Purpose

Proceed to Tier 2 (Expert Review) prior to inclusion in the Risk Assessment

**Oral**  
**24 studies**  
**- 2 OECD guideline**



**10 studies**



# NANO/MICROPLASTIC PARTICLE TOXICITY STUDY ASSESSMENT TOOL (NMP-TSAT) – 10 ORAL IN VIVO STUDIES RELIABLE TO PROCEED TO TIER 2

- Amerreh, F.; Eslami, A.; Fazelipour, S.; Rafiee, M.; Zibaii, M. I.; Babaei, M. *Toxicology Research* 2019
- Amerreh F; Babaei M, Eslami A, Fazelipour S, Rafiee M *Environ. Pollut.* 2020
- An R, Wang X, Yang L, Zhang J, Wang N, Xu F, Hou Y, Zhang H, Zhang L. *Toxicology* 2021
- Deng Y, Zhang Y, Lemos B, Ren H. *Sci Rep.* 2017
- Hou B, Wang F, Liu T, Wang Z. R. *Journal Hazard Materials* 2020
- Li B, Ding Y, Cheng X, Sheng D, Xu Z, Rong Q, et al. *Chemosphere* 2020
- Li, Z., S. Zhu, Q. Liu, J. Wei, Y. Jin, X. Wang and L. Zhang. *Environ. Pollut.* 2020
- Park EJ, Han JS, Park EJ, Seong E, Lee GH, Kim DW, et al. *Toxicology Letters* 2020
- Wei, J., X. Wang, Q. Liu, N. Zhou, S. Zhu, Z. Li, X. Li, J. Yao and L. Zhang. *Environ. Toxicol.* 2021
- Xie, X., T. Deng, J. Duan, J. Xie, J. Yuan and M. Chen. *Ecotoxicol. Environ. Safety.* 2020



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Adequate Subject Matter  
Expertise during Journal  
Submission Peer Review?

# DENG ET AL., 2017 – SCIENTIFIC PEER REVIEW/TIER 2 EVALUATION

Archives of Toxicology (2019) 93:217–218  
<https://doi.org/10.1007/s00204-018-2383-9>

LETTER TO THE EDITOR, NEWS AND VIEWS

Plausibility of microplastic uptake in a paper by Deng et al reports 7:46687, 2017

Linda Böhmert<sup>1</sup> · Valerie Stock<sup>1</sup> · Albert Braeuning<sup>1</sup>

Archives of Toxicology (2019) 93:219–220  
<https://doi.org/10.1007/s00204-018-2367-9>

BfR

GUEST EDITORIAL

Uptake of microplastics and related health effects: a critical discussion of Deng et al., Scientific reports 7:46687, 2017

Albert Braeuning<sup>1</sup>

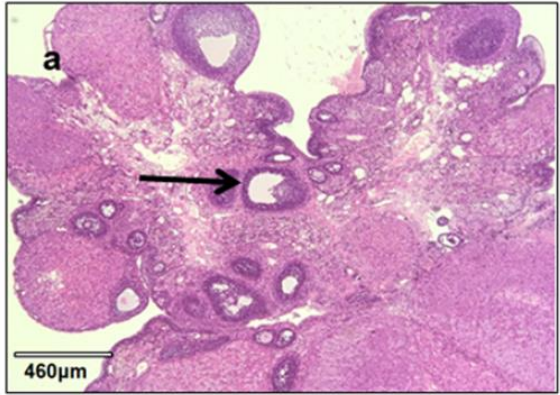
- Deng et al. concluded their data suggest widespread health risks of exposure to microplastics.....study drawbacks have been raised
- Potential adversity cannot be evaluated due to lack of details
- Concerns regarding causality: Biological plausibility, Coherence of evidence
- Conclusion: “a number of issues prevent the usage of the data....for the estimation of gastrointestinal uptake and potential health risks associated with the oral uptake of microplastics”

# TIER 2 EXPERT EVALUATION NECESSARY PRIOR TO INCLUSION IN THE RISK ASSESSMENT

Tier 2  
Expert  
Evaluation

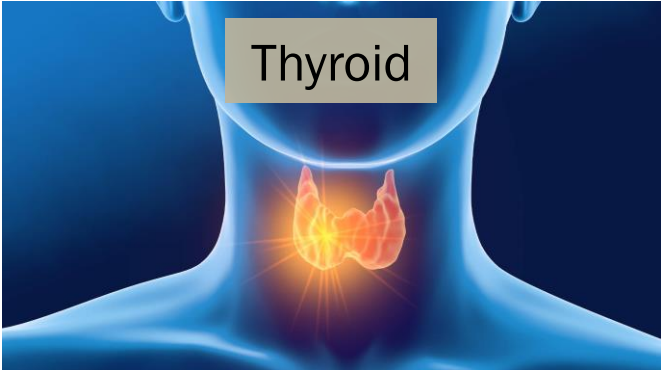
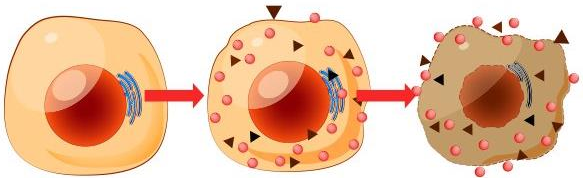
Individual  
Studies +  
Overall  
Weight of  
Evidence

Female &  
Male Repro.



An et al., 2021

Oxidative  
Stress

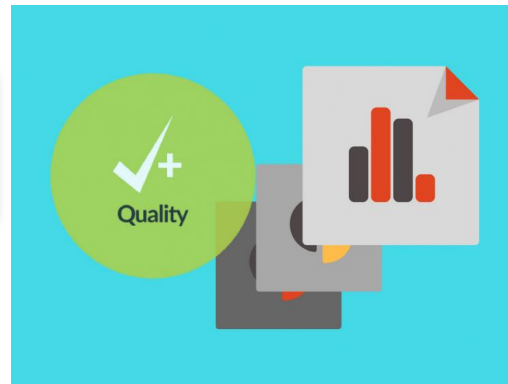
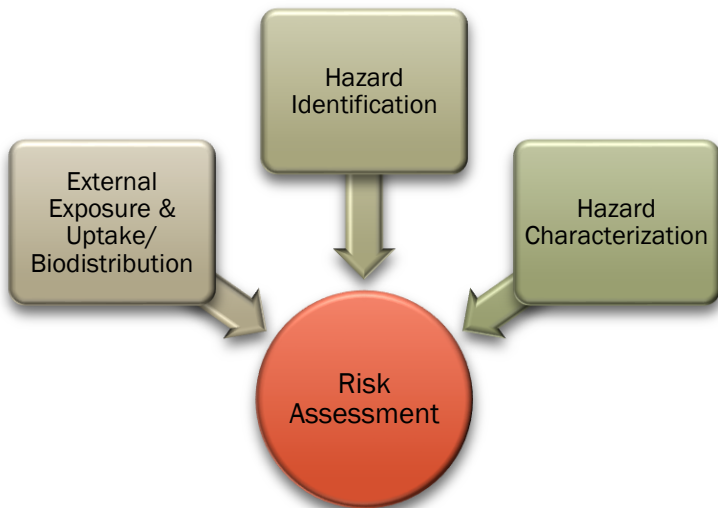
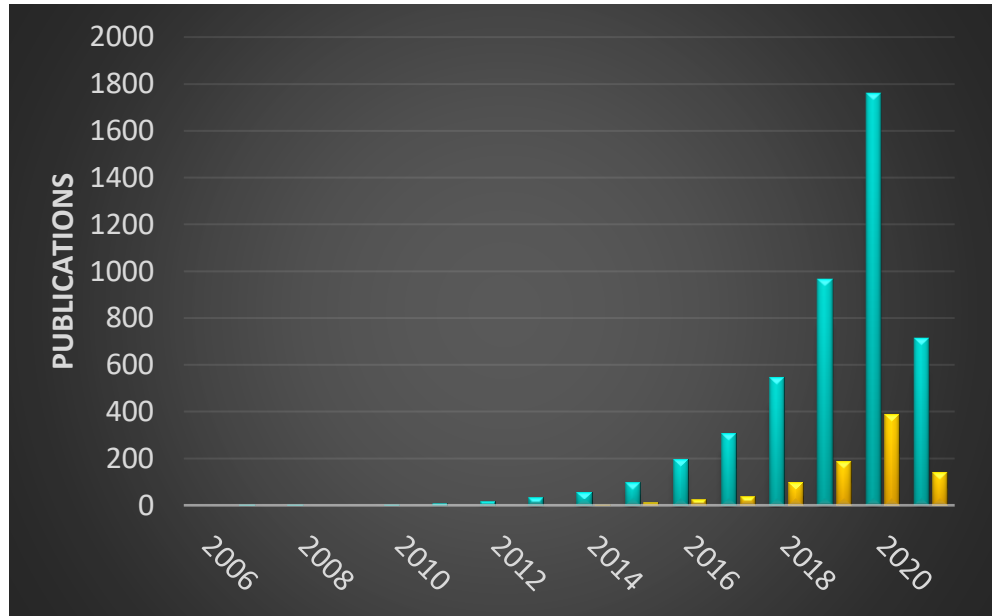




# NANO/MICROPLASTIC PARTICLE TOXICITY STUDY ASSESSMENT TOOL (NMP-TSAT) – 10 ORAL IN VIVO STUDIES RELIABLE TO PROCEED TO TIER 2

	Needed Improvements	2019
■ Ame Polystyrene A.; Fazelipour,		
■ Ame Polystyrene I, Eslami A, Fa	Particles not fit-for-purpose	
■ An F Polystyrene L, Zhang J, Wa	Equipment calibration, protein ligand substrate	
■ An F Polystyrene L, Zhang J, Wa	Test material purity unknowns: particle, unreacted	
■ Den Polystyrene mos B, Ren H.	monomers, surfactants/dispersants, vehicle (e.g.	
■ Hou Polystyrene T, Wang Z. R. J	Ethanol)	
■ Li B, Polystyrene X, Sheng D, Xu	<u>Particle characteristics</u> insufficiently reported	
■ Li, Z Polystyrene J. Wei, Y. Jin, >	Particle surface chemistry, microbial contamination	
■ Par Polyethylene k EJ, Seong E,	<u>Experimental design</u> insufficiently reported	
■ Wei, Polystyrene Liu, N. Zhou, S	Particle stability, homogeneity, internal dose confirmation	
■ Xie, Polystyrene uan, J. Xie, J. Yuan and M. CHEN. <i>ECOTOXICOL. Environ. Safety.</i> 2020	<u>Applicability to risk assessment</u> insufficiently reported	
	Environmental relevance of particle tested or exposure	
	scenario	

# CONCLUSIONS



## Nano/Microplastic Particle Toxicity Study Assessment Tool (NMP-TSAT)

Tier 1 Screen

