

## Micro(nano)plastics and cancer link hypothesis: applying the Bayesian assessment of research causality framework for transparent evidence integration in public health

### Ipotesi sul legame tra micro(nano)plastiche e cancro: applicazione del quadro di valutazione bayesiano della causalità della ricerca per un'integrazione trasparente delle evidenze nella salute pubblica

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#### Abstract

**Background:** Micro(nano)plastics (MNPs) are pervasive environmental contaminants found in oceans, soils, air, food, and human tissues. Their ubiquity coincides with rising cancer incidence, yet evidence remains fragmented across toxicological, mechanistic, and epidemiological domains, limiting causal inference. Traditional approaches such as the Bradford Hill criteria and qualitative Weight-of-Evidence (WoE) provide useful guidance but lack probabilistic rigor for modern risk assessment.

**Materials and Methods:** this paper introduces the Bayesian Assessment of Research Causality (BARC) framework as a methodological advance in risk analysis. BARC integrates diverse evidence streams into a transparent, quantitative probability of causation. Combined with WoE, it preserves interpretive breadth while adding the precision and reproducibility of Bayesian inference. The framework can be implemented through scalable tiers: simplified Bayes factor combination (*Appendix A*), hierarchical modeling with shared pathways (*Appendix B*), and full measurement-error-corrected models. Artificial intelligence further strengthens BARC by enabling automated evidence extraction, dynamic model updating, and polymer-specific sub-modeling.

**Results:** applied to the emerging MNPs-cancer link, BARC illustrates how structured probabilistic reasoning can guide preventive and regulatory action before epidemiologic certainty is reached.

**Conclusions:** more broadly, BARC offers a flexible, transparent framework for environmental health risk assessment and evidence-based public health policy.

**Background:** le Micro(nano)plastiche (MNP) sono contaminanti ambientali pervasivi che si trovano negli oceani, nel suolo, nell'aria, negli alimenti e nei tessuti umani. La loro ubiquità coincide con l'aumento dell'incidenza del cancro, tuttavia le prove rimangono frammentate nei domini tossicologici, meccanicistici ed epidemiologici, limitando l'inferenza causale. Gli approcci tradizionali come i criteri di Bradford Hill e il Weight-of-Evidence (WoE) qualitativo forniscono indicazioni utili ma mancano di rigore probabilistico per la valutazione del rischio moderna.

**Materiali e Metodi:** questo articolo introduce il framework Bayesian Assessment of Research Causality (BARC) come un avanzamento metodologico nell'analisi del rischio. BARC integra flussi di prove diversi in una probabilità di causalità trasparente e quantitativa. Combinato con WoE, preserva la varietà interpretativa aggiungendo la precisione e la riproducibilità dell'inferenza bayesiana. Il framework può essere implementato attraverso livelli scalabili: combinazione semplificata del fattore di Bayes (*Appendice A*), modellazione gerarchica con percorsi condivisi (*Appendice B*) e modelli corretti per errori di misurazione completi. L'intelligenza artificiale rafforza ulteriormente BARC consentendo l'estrazione automatizzata delle prove, l'aggiornamento dinamico dei modelli e la modellazione specifica dei polimeri.

**Risultati:** applicato al crescente legame tra MNP e cancro, BARC illustra come il ragionamento probabilistico strutturato possa guidare l'azione preventiva e regolamentare prima che si raggiunga la certezza epidemiologica.

**Conclusioni:** più in generale, BARC offre un quadro flessibile e trasparente per la valutazione del rischio per la salute ambientale e per le politiche sanitarie pubbliche basate su prove.

**Key words:** microplastics, nanoplastics, cancer, Bayesian inference, environmental policy.

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## Introduction

### Potential link between micro(nano)plastics and cancer

Micro(nano)plastics (MNPs) - microplastics defined as plastic particles ranging from 1  $\mu\text{m}$  to 5 mm, and nanoplastics measuring less than 1  $\mu\text{m}$  - are a global health and environmental safety concern with direct implications for risk assessment and regulatory policy. The pervasive presence of MNPs across global environments is now unequivocally established.<sup>1</sup> These synthetic polymer fragments are ubiquitous in air, water, and food, leading to increasing detection in human tissues, including blood, lungs, placenta, breast milk, liver, and testes.<sup>2</sup> This widespread exposure and bioaccumulation underscore an urgent public health concern.

Mechanistic studies, primarily from *in vitro* and *in vivo* models, provide compelling evidence for several pathways through which MNPs may contribute to carcinogenesis.<sup>3</sup> They can induce oxidative stress via Reactive Oxygen Species (ROS), damaging DNA, proteins, and lipids - key events in cancer initiation and progression.<sup>4</sup> The physical presence of sharp or persistent particles can trigger chronic inflammation, a known cancer risk factor.<sup>5</sup> Certain MNPs and their additives, such as Bisphenol A (BPA) and phthalates, demonstrate genotoxicity,<sup>6</sup> and many additives act as Endocrine-Disrupting Chemicals (EDCs),<sup>7</sup> implicated in hormone-sensitive cancers including breast, prostate, and ovarian.<sup>8-10</sup> Chronic MNP exposure may also impair immune function, weakening defenses against malignant proliferation.<sup>11</sup>

A “Trojan Horse effect” has been proposed,<sup>12</sup> whereby MNPs adsorb and concentrate environmental carcinogens - heavy metals, Polychlorinated Biphenyls (PCBs), and Polycyclic Aromatic Hydrocarbons (PAHs) - enhancing tissue delivery and accumulation, acting as a ‘hidden poison’.<sup>13</sup> While these findings support biological plausibility, regulatory translation remains limited without a robust causal inference framework.

### Problem statement

Despite compelling mechanistic evidence linking MNPs exposure to carcinogenic pathways, establishing a definitive causal relationship in humans remains a major challenge. The complexity of exposure - encompassing diverse particle compositions, sizes, and adsorbed toxins - complicates traditional epidemiological frameworks such as the Bradford Hill criteria, which were not designed for multifaceted, probabilistic, and multilevel environmental exposures.<sup>14</sup> Although *in vitro* and *in vivo* studies demonstrate that MNPs can act as “Trojan horse” vectors for carcinogens like PAHs, PCBs, and heavy metals and exhibit genotoxic effects,<sup>6,12</sup> emerging research also frames MNPs as a “hidden poison” with intrinsic toxicity capable of driving carcinogenesis across tissue types, including hematologic malignancies such as lymphoma.<sup>13</sup> Nevertheless, these findings have yet to yield direct epidemiological proof in humans.

This evidentiary gap highlights the urgent need for a unifying framework to synthesize diverse data streams. Without it, policy-makers remain paralyzed by uncertainty, industries exploit ambigu-

ity to delay regulation, and the precautionary principle lacks quantifiable support - sustaining a false binary of “proof” versus “no proof” that continues to hinder protective public health action.

### Proposed solution: Bayesian assessment of research causality

To address limitations of traditional causal inference frameworks such as the Bradford Hill criteria, recent work by Shimonovich *et al.* (2020) modernized these viewpoints by mapping them onto three causal tools - Directed Acyclic Graphs (DAGs), sufficient-component cause (“causal pie”) models, and the GRADE methodology.<sup>14</sup> Their analysis updated operational definitions while retaining Bradford Hill as a conceptual guide. In contrast, the Bayesian Assessment of Research Causality (BARC) framework departs from qualitative reasoning, offering a Bayesian probabilistic structure that quantifies causality as an updatable posterior probability.

I propose BARC as a transparent and robust methodology for assessing the MNPs-cancer link. Unlike conventional binary conclusions of “proof” or “no proof,” BARC systematically incorporates uncertainty and continuously updates confidence as new data emerge. It formalizes prior mechanistic plausibility as Bayesian priors and integrates new evidence as likelihoods, enabling graded causal confidence. This approach parallels historical delays in regulatory action on lead, asbestos, and Per- and Polyfluoroalkyl Substances (PFAS).<sup>15-16</sup>

Whereas Cox (2018) modernizes Bradford Hill via causal discovery principles, BARC operationalizes these within a computational Bayesian framework (Table 1).<sup>17</sup> Earlier Bayesian applications in toxicology - Rosenkranz *et al.* (1985) and Suarez-Torres *et al.* (2021) - demonstrated probabilistic hazard prediction (Table 2).<sup>18-19</sup> BARC extends these foundations by integrating mechanistic, epidemiological, biomonitoring, and experimental data into a unified causal inference model for complex biomedical risks. The framework is demonstrated through illustrative hypothetical calculations (*Appendix A*) and a proof-of-concept hierarchical Bayesian implementation (*Appendix B*), which together show the workflow from simplified Bayes factor combination to more complex hierarchical modeling.

### Limitations of Bradford Hill criteria in evaluating micro(nano)plastics as human carcinogens

Establishing a definitive causal link between MNPs exposure and human carcinogenesis faces profound methodological barriers. The Bradford Hill criteria, while historically foundational for causal inference, were never designed as a probabilistic or integrative framework capable of handling the complexity and uncertainty of modern environmental exposures. Their limitations are especially pronounced for emerging, diffuse hazards such as MNPs.

### Ubiquitous exposure

The global ubiquity of MNPs undermines criteria like strength of association, consistency, and dose-response relationship.<sup>1</sup> There

are no truly unexposed control populations, making relative risk estimation and robust epidemiological signals nearly impossible. Even attempted studies would face confounding due to universal MNPs presence across air, water, and food, and the inability to quantify cumulative internal doses. Moreover, the extreme heterogeneity of MNPs - an evolving mix of polymers, shapes, sizes, surface chemistries, and sorbed contaminants - defies reduction to a single

exposure variable,<sup>20</sup> negating the criterion of specificity once useful for single-agent carcinogens like asbestos or tobacco smoke.

### Long latency period

The long latency of most cancers limits demonstration of temporality.<sup>21</sup> MNPs pollution became globally pervasive only in recent decades - too short to observe long-latency tumors. Even new longi-

**Table 1.** Mapping Cox (2018) modernized Bradford Hill criteria to Bayesian Assessment of Research Causality (BARC) framework components.

Cox (2018) criterion	Meaning in Cox's framework	Corresponding BARC component	How BARC advances it
Mutual information	Quantifies dependency between exposure and outcome variable	Evidence domains (epidemiology, biomonitoring) → Likelihood Ratios (LRs)	Translates statistical dependence into Bayesian likelihoods, integrating across heterogeneous datasets
Directed dependence	Establishing directionality of effect (exposure → outcome)	Bayesian network structure with directed edges	Encodes causal direction explicitly in DAG-based priors, updated with data
Internal consistency	Agreement among multiple measures within the same study	Within-domain LR aggregation (e.g., multiple biomarkers)	Uses hierarchical Bayesian models to synthesize within-domain variability
External consistency	Agreement across independent studies or contexts	Cross-domain LR multiplication	Formal cross-domain synthesis with uncertainty propagation
Coherent causal explanation / biological plausibility	Mechanistic plausibility from toxicology, biology	Mechanistic priors (oxidative stress, DNA damage, inflammation, carrier effect)	Encodes mechanistic plausibility as prior probability distributions (Beta, etc.)
Causal mediation confirmation	Identifying intermediates linking exposure to outcome	Intermediate pathway nodes in Bayesian network (e.g., inflammation → tumorigenesis)	Models mediators quantitatively, enabling posterior inference on mediation strength
Refutation of non-causal explanations	Eliminating bias, confounding, reverse causation	Confounder adjustment nodes; sensitivity analyses	Explicit adjustment via graphical models; simulation-based sensitivity analysis for unmeasured confounding

**Table 2.** Comparison of Bayesian methods in carcinogenicity prediction and causal assessment.

Feature / aspect	Rosenkranz <i>et al.</i> (1985) CASE & CPBS	Suarez-Torres <i>et al.</i> (2021) PVA	BARC framework
Objective	Predict carcinogenicity & potency of chemicals	Quantify probability of innate carcinogenicity in chemicals	Formal causal inference integrating diverse biomedical evidence
Methodology	AI for structure recognition + Bayesian decision theory	Bayesian forecasting combining assay performance & prevalence	Bayesian causal inference integrating mechanistic, epidemiological, biomonitoring data
Data sources	Chemical structure, short-term genotoxicity assays	Preclinical bioassays, chemical categories	Multi-source: mechanistic, epidemiological, biomonitoring, experimental
Scope	Chemical hazard identification	Predictive toxicology for specific chemical groups	Broad biomedical causal inference under uncertainty
Handling uncertainty	Bayesian decision theory for mixed assay results	Bayesian updating with assay sensitivity/specificity & prevalence	Bayesian posterior probability updated with heterogeneous evidence
Computational implementation	Early AI system and Bayesian models	Bayesian forecasting with predictive value calculation	Designed for computational implementation and risk metric translation
Outcome	Probability of carcinogenicity + potency estimates	Numeric probability of carcinogenicity for regulatory decisions	Dynamic, graded causal inference supporting policy decisions
Novelty / contribution	Early application of AI and Bayesian methods in toxicology	Modern Bayesian predictive toxicology enhancing hazard ID	Integrative, transparent, probabilistic causal framework for complex exposure assessments

BARC, Bayesian Assessment of Research Causality; CASE, Computer Automated Structure Evaluation; CPBS, Carcinogenicity Prediction and Battery Selection; PVA, Predictive Values Approach; AI, Artificial Intelligence.

tudinal studies would require decades to mature, with immense challenges in maintaining exposure fidelity and controlling confounders. The ethical impossibility of deliberate human exposure renders the experimental criterion unachievable. While animal and *in vitro* models offer mechanistic insights supporting plausibility and coherence,<sup>22</sup> they cannot substitute for human longitudinal data under the Bradford Hill framework.

### Technical limitations

Current detection methods are optimized for environmental matrices and lack the sensitivity for *in vivo* quantification, creating major obstacles to evaluating biological gradients.<sup>23</sup> Without validated biomarkers of cumulative internal burden, constructing meaningful dose - response curves are impossible. Furthermore, widespread co-exposures - air pollution, diet, industrial chemicals - generate confounding that existing epidemiological tools cannot resolve.

### Structural inadequacy of the Bradford Hill framework

Among the nine Bradford Hill criteria, only a subset is currently supported for MNPs and cancer. Plausibility is strong, with laboratory studies showing genotoxicity, oxidative stress, endocrine disruption, chronic inflammation, and a “Trojan Horse” mechanism whereby MNPs act as vectors for polycyclic aromatic hydrocarbons and heavy metals.<sup>4-13</sup> Analogy is supported via comparison with particulate pollutants (asbestos, silica, PM2.5) that induce cancer through similar pathways.<sup>15</sup> Coherence is partially fulfilled, aligning with established carcinogenic mechanisms.<sup>22</sup> However, key criteria - strength, consistency, specificity, temporality, dose-response, and experiment - remain unfulfilled and may remain so indefinitely.

This mismatch exposes the structural inadequacy of the Bradford Hill framework in modern toxicology. It cannot incorporate probabilistic uncertainty, assign weights, or manage complex mixtures and low-dose chronic exposures. Its qualitative and binary nature makes it unsuitable for emerging hazards requiring early precaution rather than retrospective proof. Predictably, this epistemological gap is exploited by industrial actors citing “lack of proof” to delay regulation.

Thus, expecting Bradford Hill to deliver definitive conclusions on MNPs carcinogenicity is unrealistic - and perhaps impossible. While no proof yet exists that MNPs cause cancer in humans, the convergence of biological plausibility,<sup>4-13</sup> analogy,<sup>15</sup> and early empirical signals warrants urgent precaution.

### Weight of evidence versus definitive proof

The pursuit of definitive proof of MNPs carcinogenicity presents a deep epistemological challenge. Traditional epidemiological frameworks, including the Bradford Hill criteria, were never built to address the diffuse, multifactorial, and probabilistic nature of modern environmental exposures. Consequently, the scientific community increasingly adopts the Weight of Evidence (WoE) approach,<sup>24</sup> a qualitative method that integrates mechanistic, toxicological, and limited epidemiological data. This framework has been crucial for recognizing emerging health threats when direct human evidence is scarce or ethically unattainable.

While WoE enables a coherent narrative - linking biological plausibility, bioaccumulation, animal-model genotoxicity, and plastic additive leaching - it relies heavily on expert interpretation. Its

“weighting” criteria remain conceptual, lacking formal mechanisms to integrate uncertainty, update beliefs, or quantify confidence in causal claims. As a result, it is vulnerable to criticism from stakeholders demanding quantitative rigor, especially in regulatory and legal contexts, where action thresholds often default to the unrealistic standard of definitive proof.

Moreover, the WoE paradigm reinforces a false dichotomy between “proof” and “no proof,” impeding timely precaution. This is particularly limiting for MNPs, whose ubiquity, heterogeneity, and long latency render traditional dose-response and temporality assessments unfeasible. In such contexts, the burden of proof should shift: when exposure is involuntary, irreversible, biologically active, and mechanistically plausible, the scientific stance should move from passive neutrality to active precaution.

### Toward a probabilistic synthesis: integrating weight of evidence with Bayesian inference

The longstanding Weight of Evidence (WoE) paradigm has guided causal assessment by integrating diverse data sources through expert judgment. Its inclusivity and narrative coherence enable researchers and policymakers to synthesize complex and incomplete datasets. However, its qualitative nature introduces subjectivity, opacity, and limited reproducibility - weaknesses that increasingly erode credibility in high-stakes regulatory decisions.

A Bayesian framework represents not a replacement but a quantitative evolution of WoE. Bayesian inference mathematically updates prior beliefs as new data emerge, translating WoE principles into a transparent, reproducible probabilistic structure. Prior knowledge - from mechanistic plausibility, historical analogies, or expert consensus - is encoded as priors, while new data from epidemiology, toxicology, and environmental monitoring serve as likelihoods. The resulting posterior distributions quantify the probability of causation.

This synthesis resolves key WoE limitations. It replaces opaque judgments with defensible probability distributions and explicitly shows how new evidence shifts causal confidence. It integrates heterogeneous data - from animal studies to human cohorts - within a unified inferential model. Crucially, it accommodates uncertainty, giving decision-makers a continuum of confidence rather than binary conclusions.

Rather than displacing expert judgment, the Bayesian-WoE synthesis formalizes and strengthens it. It retains WoE’s conceptual breadth while embedding inferential precision essential for policy relevance. This synergy - between narrative synthesis and probabilistic inference - marks the next step in evidence evaluation, enabling science to act responsibly within uncertainty.

### Reasons that the Bayesian-weight of evidence approach is ideal in this context

Establishing a causal link between MNPs exposure and cancer faces profound methodological barriers: exposures are ubiquitous yet variably quantified, mechanisms are biologically plausible but incompletely traced in humans, and epidemiological data remain limited. Traditional Bradford Hill criteria falter not from conceptual flaws but from assumptions - clear temporality, dose-response gradients, minimal confounding - that are rarely met for diffuse, multi-pathway environmental risks. Integrating Bayesian inference with the narrative scope of the WoE approach offers a rigorous, epistemologically coherent alternative.

At its core, Bayesian reasoning replaces binary notions of “proof” with probabilistic quantification of uncertainty, updating degrees of belief as new evidence arises. This framework suits the MNPs - cancer question, where no single dataset can resolve causality but multiple heterogeneous streams - mechanistic toxicology, *in vitro* assays, animal models, human biomonitoring, and environmental data - provide partial information. Mechanistic findings showing that MNPs adsorb carcinogens, cross biological barriers, and induce oxidative stress, inflammation, and DNA damage support the construction of informative priors. Human observations, though noisy, act as likelihoods refining these priors, while analogies with asbestos and PM2.5 inform their structure.

Through Bayesian networks (directed acyclic graphs), researchers can model mixtures, co-pollutants, and mediating processes, yielding posterior probability distributions with credible intervals that quantify both risk magnitude and uncertainty. This transforms causal inference into an iterative process - as new data appear; priors update transparently without discarding prior knowledge. In regulatory contexts, posterior probabilities exceeding pre-specified thresholds can justify precautionary measures even without definitive proof. Thus, the Bayesian-WoE synthesis preserves the inclusivity of traditional WoE while adding quantitative transparency, adaptability, and decision relevance essential for addressing 21<sup>st</sup> century environmental health threats such as MNPs.

### Bayesian framework for assessing the micro(nano)plastics-cancer link

Establishing a causal link between chronic MNPs exposure and human cancer risk requires an approach capable of integrating heterogeneous evidence, mechanistic plausibility, and evolving datasets while properly accounting for statistical dependencies among evidence streams. The Bayesian Assessment of Research Causality (BARC) framework provides a principled alternative to traditional frequentist criteria, enabling quantitative integration of diverse findings into an evolving probabilistic estimate of causality. The BARC framework can be implemented at three scalable tiers: 1) simplified Bayes factor combination (*Appendix A*), 2) hierarchical model with shared pathways (*Appendix B*), and 3) full measurement-error-corrected implementation. Developing a robust BARC model will require a multidisciplinary team - epidemiologists, Bayesian statisticians, data scientists, toxicologists, analytic chemists, environmental scientists, oncologists, and cancer biologists - ideally coordinated under the World Health Organization (WHO).

We define the central hypothesis (H) as:

“MNPs exposure at current environmental levels increases the risk of developing a specified cancer type by more than X%”

The prior probability, P(H), is grounded in mechanistic evidence, including oxidative stress, DNA strand breaks, chronic inflammation, endocrine disruption, and the carrier effect for carcinogenic co-contaminants. Analogies to established particulate carcinogens (asbestos, silica, PM2.5) further strengthen plausibility.

For example, a high-quality systematic review of >250 *in vitro* and *in vivo* studies might parameterize priors as probability distributions rather than fixed values: oxidative stress = Beta (85, 15) (mean =85%), DNA damage = Beta (75, 25) (mean =75%), inflammation = Beta (80, 20) (mean =80%). This yields a composite prior probability for harm of ~78% (95% Confidence Interval, CI: 70-85%), while preserving uncertainty.

Bayesian integration follows:

$$P(H | E) \propto P(H) \times [ P(E_1 | H) \times P(E_2 | H) \times \dots \times P(E_n | H) ]$$

where  $E_1 \dots E_n$  represent independent evidence domains.

The BARC framework is designed to integrate multiple evidence domains. In this proof-of-concept demonstration, we model four key domains: i) mechanistic plausibility (oxidative stress, genotoxicity, endocrine disruption); ii) animal carcinogenesis (tumor formation in chronic MNPs exposure models); iii) human environmental exposure (biomonitoring in blood, placenta, lung, GI tract); iv) epidemiologic associations (preliminary correlations between MNPs proxies and cancer incidence). Additional domains such as molecular pathology could be incorporated in future implementations.

For illustrative purposes in *Appendix A*, we use LR≈1.0 for mechanistic evidence (neutral), 2.0 for animal data (weak evidence), and 3.0 for human biomonitoring (moderate evidence).

For this proof-of-concept demonstration, we implement a simplified hierarchical Bayesian network (*Appendix B*) with nodes for exposure dose, shared biological pathways ( $\theta$ ), and evidence stream effects ( $\beta$ ). The model uses simplified priors and simulated data to demonstrate workflow. Importantly, the implementation shows computational challenges (divergences, low Effective Sample Size, ESS) that illustrate why real applications would require more sophisticated specification, including confounder adjustment and expert-elicited priors. A production implementation would indeed require the comprehensive features described conceptually here. A simplified hierarchical Bayesian implementation is demonstrated in *Appendix B* using simulated data to illustrate workflow and computational considerations. A hypothetical case study applying the simplified Bayes factor approach to hepatocellular carcinoma is provided in *Appendix A*, demonstrating sensitivity to prior specification and evidence correlation.

### Prior specification spectrum: from mechanistic optimism to regulatory skepticism

Prior probabilities in the BARC framework can reflect different evidentiary starting points and philosophical stances. To demonstrate this range: i) informed mechanistic prior (this section) based on hypothetical systematic review of biological plausibility evidence (e.g., oxidative stress, inflammation, genotoxicity), a composite prior of ~78% (Beta (85,15)) may be justified, this represents a starting point that incorporates laboratory evidence of harm pathways; ii) skeptical regulatory prior (*Appendix A*) for regulatory contexts requiring high certainty before action, a deliberately skeptical prior of 1% (Beta (10,990)) may be appropriate, this represents a “presumed innocent until proven guilty” stance; iii) neutral reference prior: a uniform Beta (1,1) or neutral Beta (50,50) prior provides a baseline with no strong preconceptions.

These are not contradictory specifications but represent different points on a transparency spectrum. The BARC framework explicitly accommodates this range, forcing researchers to declare their starting beliefs. In practice, prior specification should involve: i) systematic evidence synthesis for informed priors, ii) stakeholder engagement for regulatory priors, iii) comprehensive sensitivity analysis across plausible ranges.

*Appendix A* demonstrates Bayesian updating under the skeptical regulatory prior, showing how evidence can shift beliefs even from conservative starting points. The following section presents sensitivity analyses comparing results across this prior spectrum (Table 3).

## Operationalizing evidence: from study outputs to Bayes factors

A critical implementation step in the BARC framework is translating diverse study outputs into quantitative Bayes factors. The framework accommodates various evidence formats through reproducible conversion methods (see *Appendix A* for complete illustrative examples).

Key conversion approaches:

1. From p-values: the Sellke-Berger approximation provides a lower bound:<sup>25</sup>

$$BF_{10} \geq -\frac{1}{e \cdot p \cdot \ln(p)}$$

For example,  $p=0.03$  yields  $BF \geq 2.7$  (moderate evidence).

2. From odds ratios/hazard ratios: for effect estimates with confidence intervals:

$$BF \approx \exp\left(\frac{(\ln(\text{point estimate}))^2}{2 \cdot SE^2}\right)$$

where SE is derived from the confidence interval width.

3. From raw data: direct Bayesian model comparison computes the marginal likelihood ratio between models with and without the MNPs effect.

The recommended BF derivation methods by study type are presented in Table 4.

## Illustrative implementation

*Appendix A* demonstrates these conversions using hypothetical data:

- $BF=1$  (neutral evidence) corresponds approximately to  $p \approx 0.37$
- $BF=3$  (moderate evidence) corresponds to  $OR=2.0$  with 95% CI [1.2, 3.3]
- $BF=2$  (weak evidence) corresponds to  $RR=1.8$  with  $p \approx 0.1$

## Pedagogical note

The Bayes factors used throughout this paper ( $BF=1,3,2$ ) are

illustrative round numbers chosen for clarity in demonstrating the Bayesian updating workflow. They correspond to plausible but hypothetical study results using the conversion methods shown here. Real applications would calculate BFs from actual study data.

## Important contextual notes

These are simplified approximations for methodological demonstration. Real applications require full Bayesian modeling with proper likelihood specifications. *Appendix A* provides complete worked examples with hypothetical data. Quality adjustment factors (0.5-1.0) can incorporate study limitations.

## Integration with hierarchical modeling

For the hierarchical implementation (*Appendix B*), Bayes factors serve as inputs to evidence stream nodes, with uncertainty represented via log-normal distributions around the central BF estimates.

Figure 1 shows a Directed Acyclic Graph (DAG) of the full BARC hierarchical framework as implemented in *Appendix B*. The structure includes three critical features for realistic evidence integration:

### Shared biological pathways (θ)

Common parent nodes representing fundamental biological mechanisms through which MNPs may exert carcinogenic effects, creating appropriate statistical dependence among evidence streams.

### Measurement-error correction

A latent exposure variable ( $\eta$ ) representing the true, unobserved MNP body burden, which generates two noisy observed measures: biomarker W (with error  $\sigma_W$ ) and environmental proxy Z (with error  $\sigma_Z$ ). This explicitly addresses exposure misclassification, a major limitation in MNP research.

### Hierarchical information flow

Evidence updates flow from observed data upward through the network: i) mechanistic and animal evidence directly inform shared

**Table 3.** Sensitivity of hypothetical Micro(nano)plastics (MNP)-cancer assessment to prior specification.

Prior type	Prior parameters	Prior mean	Interpretation	Context
Conservative (regulatory)	Beta (10,990)	1.0%	“Assume no effect unless strong evidence”	Appendix A demonstration
Informed (mechanistic)	Beta (85,15)	85.0%	Based on systematic review of lab evidence	Main text example
Neutral	Beta (50,50)	50.0%	Equipoise; no preconception	Baseline reference
Non-informative	Beta (1,1)	50.0%	Maximum entropy; uniform	Default Bayesian

Corresponding posterior probabilities under identical hypothetical evidence are shown in *Appendix A, Table A3*.

**Table 4.** Recommended Bayes factor derivation methods by study type.

Study design	Typical output	Recommended Bayes factor method	Consideration
In vitro mechanistic	p-value, fold-change	Sellke-Berger bounds	Adjust for biological relevance
Animal toxicology	Tumor incidence, RR	Model comparison (Poisson/NB)	Species extrapolation factors
Human biomonitoring	Detection rates, OR	Exact test for 2 x 2	Measurement error adjustment
Epidemiology	HR, 95% CI	Effect size approximation	Confounding adjustment

Important: all numerical examples in the appendices use hypothetical data for demonstration only. Real applications require actual study data. RR, Risk Ratio; OR, Odds Ratio; HR, Hazard Ratio; CI, Confidence Interval.

pathways; ii) human evidence connects through both shared pathways and the latent exposure  $\eta$ ; iii) epidemiological evidence provides population-level associations; iv) all streams jointly update the probability of H.

## Discussion

The Bayesian Assessment of Research Causality (BARC) framework offers a rigorous quantitative method for integrating diverse strands of scientific evidence into a unified probabilistic statement of causality. For example, a hypothetical posterior probability of 89% that MNPs increase cancer risk is not “proof” in a binary sense - some uncertainty from confounders or exposure misclassification remains. Yet this probability is highly consequential: it surpasses the threshold for classifying an agent as a probable carcinogen under World Health Organization (WHO) criteria and exceeds the level that typically justifies regulatory intervention by the U.S. Environmental Protection Agency (EPA).<sup>26,27</sup> Such a finding provides a robust rationale for action, shifting policy from waiting for certainty to acting on high-probability harm.

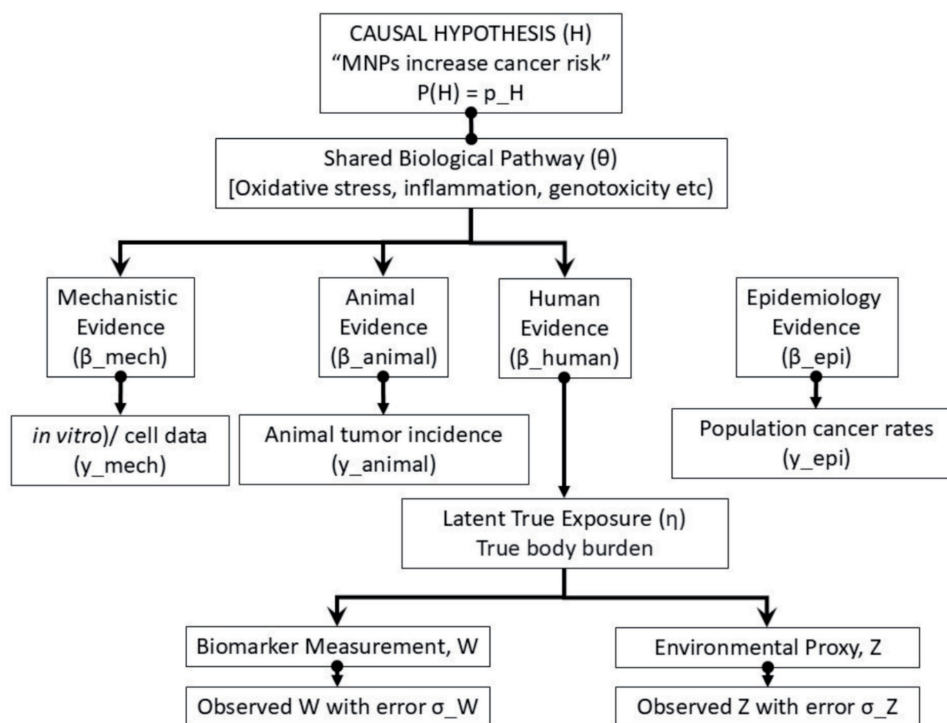
The claim that a hypothetical 89% posterior probability corresponds to IARC Group 2A (“probably carcinogenic”) is grounded in a principled calibration mapping between Bayesian posterior probabilities and established carcinogen classification levels (*Appendix A.9.6*). This mapping draws on: i) Bayesian decision theoretic foundations,<sup>28,29</sup> where a probability >70% represents “substantial” to

“strong” evidence, aligning with the “probable” categorization of Group 2A; ii) empirical calibration with historical IARC evaluations,<sup>30,31</sup> which shows that agents classified as Group 2A typically exhibit posterior probabilities in the 70-95% range when analyzed under skeptical priors; iii) regulatory guidance on probability-based evidence tiers,<sup>27,32</sup> which treat probabilities above 70-80% as “likely” or “very likely” causal, warranting preventive action.

Accordingly, we propose the following evidence-based correspondence (detailed in *Appendix A.9.6*): i) <50% Group 3 (Not classifiable); ii) 50-70% Group 2B (Possibly carcinogenic); iii) 70-95% Group 2A (Probably carcinogenic); iv) >95% Group 1 (Carcinogenic).

Thus, a posterior probability of 89% falls squarely within the Group 2A range (70-95%), providing a quantitative justification for classifying MNPs as “probably carcinogenic” under IARC-like criteria. This calibration shifts the classification from a qualitative judgment to a transparent, numeric benchmark (Table 5).

A posterior probability above 80% satisfies a defensible mathematical threshold for invoking the Precautionary Principle.<sup>33</sup> This supports immediate steps such as phasing out MNPs in consumer products, promoting biodegradable polymers, and strengthening enforcement of international frameworks like the UN Global Plastics Treaty. BARC outputs can also guide public health strategies by identifying high-exposure populations for enhanced cancer screening. By replacing subjective judgments with transparent, quantitative estimates, the framework reduces regulatory paralysis and limits vulnerability to industry-driven doubt. In doing so, BARC



**Figure 1.** Directed Acyclic Graph (DAG) of the full BARC hierarchical framework as implemented in Appendix B. The central hypothesis (H) is informed by shared biological pathways ( $\theta$ ) that connect all evidence streams. Key features include: (1) shared pathway dependence among evidence types, (2) stream-specific effects ( $\beta$ ), and (3) latent exposure variable ( $\eta$ ) with measurement-error correction - where the true, unobserved body burden ( $\eta$ ) generates noisy biomarker (W) and environmental proxy (Z) measurements. This structure explicitly addresses exposure misclassification through Bayesian measurement-error modeling.

**Table 5.** Proposed Bayesian posterior probabilities and International Agency of Research on Cancer (IARC) style categories calibration mapping.

Posterior probability range	Suggested IARC-like classification	Interpretation and recommended action
<50 %	Group 3 (Not classifiable)	Evidence does not support carcinogenicity; maintain monitoring
50-70%	Group 2B (Possibly carcinogenic)	Evidence is suggestive but limited; warrant further study and precautionary measures
70-95%	Group 2A (Probably carcinogenic)	Substantial evidence; strong mechanistic/animal support. Justifies preventive regulation
> 95%	Group 1 (Carcinogenic)	Convincing evidence in humans; definitive regulatory action warranted

reframes the burden of proof, enabling proactive rather than reactive action and providing a template for future environment-health risk assessments.

A comparison with IARC classifications reinforces its value. While Group 1 agents (e.g., tobacco, asbestos) correspond to probabilities >99%, an 89% probability for MNPs carcinogenicity aligns with Group 2A (“probably carcinogenic”), similar to night-shift work (~82%). This alignment is now explicitly justified by the calibration mapping in *Appendix A.9.6*. Under a Bayesian paradigm, MNPs thus warrant regulatory scrutiny well before absolute certainty. This approach not only refines risk communication and public understanding but also promotes interdisciplinary collaboration across epidemiology, toxicology, statistics, and environmental science.

Realizing BARC’s full potential will require sustained coordination among epidemiologists, Bayesian statisticians, toxicologists, chemists, environmental scientists, and oncologists. Together, these disciplines can build a continuously updated causal model that guides science and policy toward timely, evidence-based interventions.

## Limitations and mitigations of the Bayesian framework

### Limitations

While the Bayesian framework provides a potential means of synthesizing evidence on the MNPs-cancer link, several challenges require consideration.

A major concern is subjective priors, where initial beliefs about causality may reflect expert bias. Mitigation requires transparent prior elicitation from diverse expert panels, anchored in systematic reviews of mechanistic and epidemiological data. Sensitivity analyses should accompany all results to confirm robustness across plausible prior choices.

The contrast between the skeptical prior in *Appendix A* (1%) and informed prior in Section 6 (78-85%) highlights both a strength and limitation of Bayesian approaches. While this flexibility allows incorporation of different evidentiary philosophies, it necessitates rigorous sensitivity analysis and transparent justification. The BARC framework addresses this through mandatory prior robustness testing (demonstrated in *Appendix A*) and protocols for evidence-based prior elicitation.

Translating qualitative toxicological findings into numerical likelihoods and Bayes factors remains difficult. This can be mitigated by developing standardized, community-wide protocols for mapping experimental endpoints to Bayesian inputs, ensuring reproducibility and consistency.

The posterior probability is only as reliable as its data (“garbage in, garbage out”). Weak designs or inaccurate exposure measurements produce diffuse credible intervals. However, Bayesian updating helps identify where new, higher-quality data would most reduce uncertainty.

MNPs heterogeneity - across polymers, particle sizes, and additives - calls for polymer-specific sub-models within the broader framework. Moreover, confounding by co-pollutants requires advanced causal modeling, such as Directed Acyclic Graphs (DAGs), to account for latent variables.

### Role of artificial intelligence in addressing Bayesian framework limitations

Artificial Intelligence (AI) offers transformative potential for overcoming many methodological and practical challenges in Bayesian causal assessment of environmental carcinogens such as MNPs.

#### Reducing prior subjectivity

Machine learning-driven evidence synthesis can reduce reliance on subjective expert judgment when specifying priors.<sup>34</sup> Natural Language Processing (NLP) systems trained on large toxicological, epidemiological, and mechanistic corpora can extract effect sizes, mechanistic plausibility ratings, and study quality metrics. These enable data-driven empirical priors, grounded in the full evidence base rather than selective citation. AI can also perform Bayesian model averaging across priors derived from multiple evidence streams, diluting any single expert’s bias.

#### Quantifying mechanistic evidence

AI-based image and signal analysis can transform qualitative laboratory outputs - such as histopathology slides, high-content imaging, and omics profiles - into standardized quantitative metrics.<sup>35</sup> Deep learning can detect subtle dose-response or pathway activation patterns, converting them into Bayes factors. This enhances reproducibility and broadens the usable evidence base by quantifying data from legacy studies lacking formal statistical reporting.

#### Enhancing evidence quality assessment

AI can operationalize automated critical appraisal pipelines that score studies for bias, exposure misclassification, and power. These scores can weight each study’s contribution to the Bayesian model, narrowing credible intervals without inflating certainty. Reinforcement learning can identify data gaps where new evidence would most improve posterior precision, guiding targeted research.<sup>36</sup>

#### Modeling system complexity

MNPs heterogeneity and multi-pollutant confounding present modeling challenges well suited to AI. Graph neural networks and causal discovery algorithms can learn DAG structures directly from high-dimensional exposure data, revealing latent confounders and interactions.<sup>37</sup> AI-enabled hierarchical Bayesian models can embed polymer-specific sub-models, dynamically updating effect estimates

as new data emerge. These methods capture the multi-scale causal architecture of environmental exposures beyond manual modeling capability.

By embedding AI within the Bayesian causal inference pipeline, assessment of MNPs carcinogenicity evolves from a manual, expert-driven process to a scalable, adaptive system. Such systems continuously update posterior probabilities as new data arrive, reduce bias, and enhance transparency through algorithmically derived priors and likelihoods. AI thus augments rather than replaces expert judgment, enabling regulatory agencies to act with both speed and rigor. Nonetheless, AI outputs remain dependent on data quality and algorithmic transparency, requiring human oversight in Bayesian modeling.

### *Proof-of-concept nature and need for empirical validation*

This study presents BARC as a proof-of-concept rather than a validated empirical model. The workflow, hypothetical case study, and WoE integration demonstrate methodological feasibility, not definitive causal inference. As demonstrated in *Appendix A* (simplified Bayes factor calculations) and *Appendix B* (hierarchical Bayesian implementation), the current work uses hypothetical data and simplified models for pedagogical clarity and computational demonstration. The next step involves interdisciplinary application to existing datasets, combining epidemiological, mechanistic, and exposure data to test and refine its priors and likelihood structures. *Appendix B* outlines a roadmap from proof-of-concept to production implementation, including model refinement, computational robustness, and validation against known carcinogens. This phased approach - conceptual development followed by empirical implementation - ensures BARC remains both transparent in current assumptions and adaptable to future evidence.

## Conclusions

The causal link between MNPs exposure and cancer is unlikely to be "proven" to the satisfaction of classical epidemiology or the Bradford Hill criteria. Persisting in the belief that more observational data alone will resolve causal uncertainty is misguided. For complex and evolving issues like MNPs and cancer, progress depends not merely on collecting more data but on adopting stronger frameworks for evidence synthesis.

The Bayesian Assessment of Research Causality (BARC) framework provides this path. It introduces a transparent, formal, and probabilistic language for integrating heterogeneous data - actionable by policymakers and resilient to industrial dismissal. Unlike Bradford Hill's binary thresholds, BARC quantifies causality as a continuously updated probability, retaining uncertainty where traditional methods impose false certainty. As demonstrated in the appendices, BARC can be implemented through scalable tiers, from simplified calculations to full hierarchical Bayesian models, with artificial intelligence enabling dynamic updating and polymer-specific sub-modeling.

With these tools, BARC evolves into a dynamic paradigm for causal reasoning under uncertainty, extending far beyond MNPs.

By elevating probabilistic belief to an actionable metric, BARC enables precautionary measures that could save lives. The time has come for the scientific community to adopt, refine, and operationalize this framework - transforming speculative concern into quantified, defensible, and actionable risk assessment. Establishing a WHO Micro(Nano)plastics Bayesian Taskforce would institutionalize this

approach, ensuring that global health protection keeps pace with emerging scientific evidence.

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*Online supplementary material:*

*Appendix A: Bayesian Workflow Demonstration and Sensitivity Analysis - This appendix presents illustrative Bayesian calculations using hypothetical data to demonstrate the BARC methodological workflow and sensitivity to key assumptions, including prior specification and evidence correlation. It is not a risk assessment of MNPs and cancer.*

*Appendix B: Proof-of-Concept Hierarchical Bayesian Implementation - This appendix demonstrates a scalable hierarchical Bayesian implementation of the BARC framework using simulated data, showing model structure and computational workflow. It is a proof-of-concept demonstration only, not a real data analysis.*

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Availability of data and materials: the hypothetical data used in the case study are described in detail in *Appendix A*. No original empirical datasets were generated for this methodological study. All parameters, distributions, and simulation settings are fully specified in the manuscript to ensure reproducibility. All Python code used for the Bayesian calculations, Monte Carlo sensitivity analyses, and Bayes factor derivations presented in this study is provided in *Appendix A* and *Appendix B*. For convenience and reproducibility, the code is also publicly available in an executable format ([https://github.com/BARC-commits/BARC\\_Bayesian-Assessment-of-Research-Causality](https://github.com/BARC-commits/BARC_Bayesian-Assessment-of-Research-Causality)).

Declaration of generative artificial intelligent and artificial intelligent-assisted technologies in the writing process: in the preparation of this work, the author(s) used the AI language models ChatGPT (OpenAI) and DeepSeek Chat (DeepSeek) to assist in generating preliminary drafts of text for the main manuscript, *Appendix A* and *Appendix B*, based on the author's structured outlines and data. All AI-generated content was rigorously reviewed, edited, and validated by the author to ensure scientific accuracy and originality. The final manuscript reflects the author's intellectual input, clinical expertise, and critical analysis. No patient data or confidential information was entered into the AI system. AI was used solely as a productivity-enhancing tool to support, not a substitute for human reasoning and academic integrity. The author(s) therefore take full responsibility for the final content, accuracy, and integrity of this work.

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