

Analytical Evaluation Thresholds for Photopolymer Extractables: Coverage, Identification, Quantitation and Uncertainty

A measurement-decision framework for defensible non-targeted chemical characterisation

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Abstract

An analytical evaluation threshold (AET) is a decision threshold for chromatographic screening, not an instrument property and not a toxicological verdict. Its defensibility depends on the toxicologically based threshold supplied to the analytical study, the represented device and extraction scenario, sample-preparation factors, method coverage, response-factor variation, identification confidence and quantitation uncertainty. Photopolymer devices make these dependencies especially important because residual monomers, oligomers, photoinitiator-related species, additives, pigments, wash residues and transformation products can occupy very different chemical spaces. This review defines a non-compensatory architecture for deriving and applying an AET to photopolymer extractables. It separates the sample-domain threshold from the instrument-domain threshold, requires orthogonal coverage of volatility and polarity domains, and treats relative response factors and recovery as empirical distributions rather than universal constants. Peaks above the adjusted threshold require identification and toxicological routing; peaks below it are defensibly screened only inside a demonstrated method domain. Unknowns, poor responders, coelution and blank contamination remain explicit uncertainty. The resulting evidence package links every reported constituent to acquisition mode, identification level, quantitation basis and decision status without disclosing proprietary formulations or acceptance limits. Keywords: analytical evaluation threshold; extractables; leachables; photopolymer; non-targeted analysis; relative response factor; identification; uncertainty

1. Significance, scope and ownership

ISO 10993-18:2020 defines a stepwise framework for identifying and, where necessary, quantifying device constituents, manufacturing-introduced substances, extractables, leachables and relevant degradation products [1]. Its 2022 amendment addresses determination of an uncertainty factor for response variation [2]. An AET operationalises a toxicologically based reporting decision inside that framework, but it cannot demonstrate safety by itself.

1.1 Corpus boundary

ER-253 owns analytical threshold translation, chemical-space coverage, peak identification, quantitation and analytical uncertainty. ER-175 retains washing-system engineering; ER-181 retains post-cure engineering; ER-206 retains micro-computed-tomography metrology. ER-251 owns biological-evaluation planning; ER-252 owns cytotoxicity-test artefacts; ER-254 owns toxicological hazard, exposure and margin-of-safety assessment; ER-255 to ER-259 own application-specific biological questions; and ER-260 owns patient-specific digital traceability. ER-253 consumes a justified toxicological threshold and a frozen device state but does not create either.

2. Define the AET correctly

The AET is the concentration or amount at which a detected signal must be evaluated and routed. It is derived from a dose-based threshold and the analytical workflow. It is not identical to the limit of detection, limit of quantitation or a compound-specific exposure limit. A peak below the AET is screened only if the method demonstrably covers that chemical class and the peak is not suppressed, coeluted, subtracted as a blank without justification or represented by a response outside the validated uncertainty distribution.

3. Freeze the represented system

Record resin designation, printer and wavelength, layer schedule, wash and dry history, post-cure, support removal, finishing, sterilisation, packaging, ageing, device geometry, exposed area and mass. Define extraction vehicle, ratio, temperature, duration, agitation, vessel, headspace, replicates and storage before analysis. The same formulation can produce different extractable profiles after changes in conversion, surface area, channel accessibility or solvent history. The analytical threshold therefore belongs to a declared device-extraction-method configuration, not to a generic resin name.

4. Establish the toxicological input

The toxicologist supplies a dose-based threshold appropriate to exposure duration, route, population and constituent exclusions. Cohorts of concern and compounds requiring compound-specific handling must not be hidden inside a generic threshold. The laboratory should receive the threshold, its units, the patient-use assumptions and the maximum number of devices or contacts per interval. It should not silently reinterpret a toxicological screening value.

5. Translate dose to the sample domain

For a simple daily-use case, the threshold concentration in the extract can be represented as $AET_{sample} = DBT / (N_{day} V_{dose})$ where AET_{sample} is the unadjusted sample-domain threshold, DBT is the applicable dose-based threshold, N_{day} is the maximum number of represented devices or device-equivalents per day, and V_{dose} is the extract volume associated with one represented device-equivalent. Unit conversions, pooling and surface-area normalisation must be explicit.

6. Translate the threshold through preparation

Account for concentration, dilution, solvent exchange, split ratios, injection volume, derivatisation, recovery and any aliquot that no longer represents the whole extract. Each factor should have a direction and an evidence source. The final instrument-domain threshold is method- and preparation-specific. Copying one numerical AET across gas chromatography, liquid chromatography and headspace methods is defensible only when the different preparation and response domains have been reconciled.

7. Define the chemical-space coverage claim

Partition the anticipated chemical space by volatility, molecular mass, polarity, ionisability, thermal stability and functional class. A typical battery may require headspace gas chromatography, direct-injection gas chromatography and liquid chromatography in complementary ionisation modes, with targeted methods for inorganic or highly polar species. The 2025 experimental reference-standard study by Yun, Herath, Jin, Kim, Belton, Rufer and

Rivera Betancourt found broad response variation and no simple correlation between six physicochemical descriptors and measured relative response factors [5]. Coverage therefore requires empirical challenge compounds, not inference from one descriptor.

8. Separate detection, reporting and quantitation

Detection answers whether a signal distinguishable from background exists. Reporting applies the adjusted decision threshold. Identification assigns a chemical hypothesis with stated confidence. Quantitation estimates amount with a declared calibrant and uncertainty. These operations may have different limits. A feature can be reproducibly detected yet remain unidentifiable; an identified feature can be estimated only semi-quantitatively; a below-threshold signal can still require investigation when it belongs to an excluded chemical class.

9. Measure relative response factors

For analyte j , the relative response factor can be written $RRF_j = (A_j / C_j) / (A_{ref} / C_{ref})$ where RRF_j is the response of analyte j relative to the reference, A_j and A_{ref} are their integrated signals, and C_j and C_{ref} are their concentrations under the same acquisition conditions. Linearity, concentration range, integration and matrix effects must accompany the value. Niehuus, Renneisen, Reinschmiedt, Sievers, Schmitz and Meckelmann compared LC-MS/MS quantitation approaches across multiple polymeric medical-device materials and showed that surrogate choice materially affects estimated concentration [6]. A single universal surrogate cannot be assumed to bound every compound.

10. Derive and apply uncertainty factors

The uncertainty factor lowers the operational threshold to protect against compounds that respond less strongly than the calibrant. Jenke, Christiaens, Beusen, Verlinde and Baeten analysed a database of nearly 1,200 extractables and leachables to relate factor choice to empirical coverage [3]. Rozio, Angelini and Carrara further examined correction of detection and quantitation bias using relative-response distributions [4]. The selected factor should state the reference population, analytical modes, coverage percentile, treatment of non-detects and applicability to the current method. Increasing the factor is not a substitute for adding a missing analytical mode.

11. Qualify identification confidence

Use a documented hierarchy: confirmed identity with an authentic standard; probable identity supported by orthogonal spectral and retention evidence; tentative library match; chemical class only; or unknown. Record match metrics, diagnostic ions, retention behaviour, adduct assignment and contradictory evidence. Names generated from a single library score should not be promoted to confirmed identities. Isomeric uncertainty can be toxicologically material and should be retained until resolved.

12. Confirm high-consequence constituents

Targeted confirmation is warranted when a feature exceeds the adjusted AET, maps to a high-hazard hypothesis, has weak non-target identification or sits near a decision boundary. Authentic standards should be analysed with the same method when feasible.

Confirmation should address identity and amount separately. A retention-time match without adequate spectral selectivity does not establish identity; exact mass without reference quantitation does not establish concentration.

13. Characterise recovery and matrix effects

Perform representative spike-recovery experiments before and, where relevant, after extraction. Challenge different volatility, polarity and ionisation classes. Matrix-induced suppression or enhancement should be distinguished from extraction recovery. Poor recovery can create a false below-threshold result even when instrument response is adequate. Corrective factors must be bounded by data and should not manufacture precision beyond the experiment.

14. Control blanks and contamination

Include procedural, solvent, vessel and system blanks appropriate to each mode. Define rules for subtraction, carryover and ubiquitous laboratory contaminants before examining device data. Blank subtraction should preserve evidence: raw feature intensity, blank distribution, sample-to-blank ratio, replicate consistency and decision rationale. A peak cannot be erased merely because it appears once in a blank.

15. Address coelution and mass balance

Inspect deconvolution quality, unresolved envelopes and detector saturation. Orthogonal separation or targeted reanalysis is needed when coelution could hide a poor responder or inflate a surrogate estimate. A semi-quantitative mass balance across identified, tentatively identified and unknown features is useful as a diagnostic. It is not proof of exhaustive characterisation because nonresponsive chemical space remains possible.

16. Use non-compensatory gates

Gate	Required evidence	Blocking failure
Device state	Frozen process, geometry and ageing	Study cannot represent the claimed device
Threshold input	Dose basis, units, exclusions and use frequency	AET cannot be derived
Preparation	Traceable dilution, concentration and recovery	Instrument threshold is indeterminate
Coverage	Orthogonal methods and challenge compounds	Below-threshold claims are domain-limited
Response	Empirical RRF distribution and uncertainty factor	Poor responders can be missed
Identification	Confidence level and contradictory evidence	Toxicological routing remains unresolved
Quantitation	Calibrant, range, matrix effect and uncertainty	Exposure estimate is not decision-grade
Blanks	Predetermined subtraction and carryover rules	Reported profile can be biased

Passing one gate cannot compensate for failure of another. The result must remain unresolved until the missing evidence is obtained or the residual uncertainty is explicitly accepted by the device risk process.

17. Route analytical outcomes

Each feature should receive a status: below adjusted AET within demonstrated coverage; above threshold and identified; above threshold and unknown; targeted exception; blank-associated but retained; or analytically unresolved. The route may be toxicological assessment, confirmatory analysis, method extension, process investigation or documented exclusion. Sussman, Oktem, Isayeva, Liu, Wickramasekara, Chandrasekar, Nahan, Shin and Zheng describe the value and limitations of non-targeted medical-device analysis and emphasise the laboratory-specific nature of current practice [7]. This supports explicit method boundaries rather than claims of universal completeness.

18. Control changes and transfer

Reassess the threshold and coverage after changes in formulation, supplier, pigment, printer, wash, cure, sterilisation, packaging, geometry, extraction ratio, instrument, column, ion source, software or library. Method transfer requires comparison of response distributions and decision outcomes, not

only retention-time reproducibility. Archive raw data, processing parameters, feature tables, manual integrations, spectral evidence, calibration models and software versions so that threshold decisions can be reproduced.

19. Minimum reporting set

Report the device state; extraction design; toxicological threshold and use assumptions; AET derivation; all preparation factors; analytical modes and coverage claim; system suitability; calibration and surrogate choices; RRF and uncertainty-factor evidence; detection and quantitation limits; identification levels; blank rules; recovery and matrix effects; unknown features; exceptions; deviations and decision routes.

20. Knowledge boundary

The normative records establish the chemical-characterisation and uncertainty-factor framework [1,2]. Empirical studies demonstrate response-factor variation, surrogate dependence and the value of diversified standards [3-6]. The FDA-authored perspective explains current non-target practice and gaps [7]. None establishes that a particular photopolymer device, extraction or laboratory method is exhaustively characterised.

21. Limitations

References [1] and [2] were verified against current official ISO records; references [3-7] were verified at full-text or detailed primary-record depth. Controlled standards govern implementation. This review does not provide a product-specific threshold, disclose formulation data, set a universal uncertainty factor or replace qualified analytical and toxicological judgement.

22. Conclusions

A defensible AET is a traceable translation from toxicological dose to method-specific instrument decision. Its validity rests on a frozen device and extraction state, orthogonal chemical-space coverage, empirical response and recovery evidence, graded identification and honest uncertainty. Below-threshold decisions are meaningful only within the demonstrated method domain; unknowns and poor responders remain visible until resolved.

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