

Toxicological Risk Assessment of Photopolymer Constituents and Leachables: Exposure, Hazard, Read-Across and Margin of Safety

A constituent-level framework from analytical evidence to transparent residual-risk decisions

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Abstract

Toxicological risk assessment of a photopolymer device asks whether exposure to each relevant constituent or leachable can cause appreciable harm in the intended clinical use. The answer cannot be inferred from resin identity, an analytical pass/fail label or a single toxicity database entry. It requires a frozen finished-device state, exposure magnitude and duration, chemical identity confidence, endpoint-specific hazard evidence, route and population relevance, transparent uncertainty factors and explicit treatment of data gaps. This review defines a reproducible assessment architecture aligned with ISO 10993-17:2023 and its 2025 amendment. It separates measured quantity from patient exposure, uses a tiered hierarchy for point-of-departure selection, constrains read-across through structural, metabolic and toxicodynamic similarity, and expresses systemic or local risk with endpoint-appropriate tolerable exposure and margin-of-safety calculations. Threshold-of-toxicological-concern screening is limited by its domain and exclusions; mixture, genotoxicity, carcinogenicity, reproductive toxicity and local-contact hazards are not collapsed into one scalar. Non-compensatory gates preserve uncertainty and route unresolved constituents to additional chemistry, targeted toxicology, process control or biological evidence. No proprietary composition or product-specific acceptance limit is disclosed. Keywords: toxicological risk assessment; photopolymer; leachables; exposure; hazard; read-across; tolerable intake; margin of safety

1. Significance, scope and ownership

ISO 10993-17:2023 specifies a process for assessing toxicological risk from medical-device constituents using chemical-characterisation information and the intended exposure [1]. Its 2025 amendment is part of the current published framework [2]. ISO 10993-1:2025 places the conclusion within device biological evaluation and risk management [3].

1.1 Corpus boundary

ER-254 owns constituent-level exposure assessment, hazard appraisal, read-across, tolerable-exposure derivation and margin-of-safety interpretation. 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-253 owns AET derivation, analytical coverage, identification and quantitation; ER-255 to ER-259 own application-specific biological questions; and ER-260 owns patient-specific digital traceability. ER-254 does not substitute for those methods or for device-level benefit-risk judgement.

2. Define the assessment question

State the constituent, identity confidence, device state, patient population, contact tissue, route, frequency, duration, maximum simultaneous device use and relevant life stage. Distinguish a screening assessment from a compound-specific toxicological evaluation. The conclusion should name the endpoint and time frame. A chronic systemic conclusion does not automatically address local irritation, sensitisation, genotoxicity or a short high-concentration exposure.

3. Freeze the chemical evidence

Use the exact analytical data version, extraction or simulated-use condition, device-equivalent calculation, recovery basis and uncertainty model. Retain unknown features and tentative identities. Do not assign a favourable toxicological profile to an uncertain name. The FDA guidance of 8 September 2023 emphasises risk-based biological evaluation and representative device preparation [4]. Jurisdictional recognition and applicable editions should be checked at the time of submission.

4. Build the constituent inventory

Include formulation constituents, manufacturing-introduced substances, residual monomers and oligomers, photoinitiator-related products, colorants, stabilisers, wash residues, sterilisation residues, ageing products, degradants and analytically detected unknowns. Record source and confidence for each entry. For each substance, preserve synonyms, identifiers, stereochemistry, salt or complex form and analytical evidence. Misidentification can select the wrong hazard record and create false precision.

5. Estimate patient exposure

A simplified systemic exposure estimate can be represented as $E_{\text{patient}} = Q_{\text{device}} N_{\text{use}} F_{\text{transfer}} / M_{\text{body}}$

where E_{patient} is estimated exposure per unit body mass and time, Q_{device} is the quantity released or conservatively available from one device in that interval, N_{use} is the maximum device-equivalents used, F_{transfer} is the justified fraction reaching the patient by the relevant route, and M_{body} is the body-mass basis for the population. Units and averaging time must be explicit. Use time-resolved release when peak or repeated exposures matter. A total extractable amount divided across the entire service life can understate early exposure; assigning the total quantity to every day can overstate it. Both choices require justification.

6. Select the exposure scenario conservatively

Define central and upper-bound cases when data permit. Consider minimum body mass, maximum surface area, multiple devices, repeated procedures, renal or hepatic impairment, neonates, pregnancy and compromised barriers where relevant. Simulated-use data can be more exposure-relevant than exaggerated extraction, but only if the use model is validated. Badding, Vargas, Fortney, Cheng and Ho compared simulated-use and exaggerated BPA extraction from dialysers and obtained different exposure estimates and margins [6]; the finding is device-specific but illustrates why extraction severity must remain visible.

7. Assemble hazard evidence

Search authoritative assessments, peer-reviewed studies, curated databases and mechanistic evidence. Record the searched identity, date, endpoint, species, route, duration, dose metric, quality and relevance. Negative results require adequate power and exposure confirmation. Distinguish point-of-departure data from supporting evidence. A study can establish mechanistic plausibility without being suitable for numerical limit derivation.

8. Select the point of departure

Prefer robust human or animal data that match the endpoint, route and duration. Depending on the evidence, the point of departure can be a benchmark dose, no-observed-adverse-effect level or other justified value. Explain why the selected effect is critical and how competing studies were weighted. Parris, Martin, Stanard, Glowienke, Dolan, Li, Binazon, Giddings, Whelan, Masuda-Herrera, Bercu, Broschard, Bruen, Callis, Stults, Erexxon, Cruz and Nagao provide four compound case studies showing how dataset quality, degradation products and route extrapolation affect health-based limits [5]. Their pharmaceutical context informs method, not direct device acceptance.

9. Apply uncertainty and modifying factors

Address interspecies and intraspecies variability, duration extrapolation, database completeness, point-of-departure type, route differences and sensitive populations. Each factor should have a rationale and should not duplicate conservatism already present elsewhere. Moeller modelled oral bioavailability for thousands of medical-device constituents and evaluated an evidence-based oral-to-parenteral factor [7]. The study supports chemical-specific or analogue-informed refinement where justified; it does not authorise replacing the controlled standard or ignoring substances outside the modelled domain.

10. Constrain route-to-route extrapolation

Compare absorption, first-pass metabolism, local portal effects, distribution and elimination. Oral data may be inappropriate for parenteral or mucosal exposure without a conservative adjustment. Inhalation and dermal routes require endpoint-appropriate dosimetry. When bioavailability is unknown, state the default assumption. When modelled, record model domain, inputs, uncertainty and whether the analogue or chemical was actually represented.

11. Use read-across as a structured argument

Define source and target structures, functional groups, ionisation, physicochemical properties, impurities, metabolism, reactive intermediates and endpoint concordance. Explain differences, not only similarities. A shared scaffold is insufficient when a substituent changes reactivity or disposition. Read-across uncertainty should influence the modifying factor or trigger targeted testing. Do not use a low-hazard analogue to overwrite a structural alert without resolving the alert.

12. Use screening thresholds within their domain

A threshold of toxicological concern or toxicological screening limit can prioritise low exposures when identity, exposure and exclusion criteria are adequately addressed. It is not a universal safe dose. Cohorts of concern, high-potency toxicants, genotoxic alerts, metals, proteins, nanomaterials and poorly defined mixtures may require separate handling. Threshold screening should preserve cumulative exposure assumptions and duration. Passing a screening threshold for systemic toxicity does not automatically close local irritation or sensitisation. Document the exact screening rule, source edition, duration bin and exclusions applied to every constituent. Where a feature is only tentatively identified, the assessor should test whether each plausible identity remains inside the same screening domain; otherwise analytical confirmation is required before the threshold can carry the decision.

13. Calculate and interpret margin of safety

For a compatible endpoint and time basis, the margin can be expressed as $MOS = TI / E_{patient}$ where MOS is the margin of safety, TI is the endpoint- and duration-specific tolerable intake or comparable tolerable exposure, and $E_{patient}$ is the matched estimated patient exposure. Numerator and denominator must use compatible units, routes, averaging periods and populations. A numerical margin above unity is not self-interpreting. Confidence in identity, exposure, hazard dataset, uncertainty factors, local effects and combined exposures determines whether the margin supports a conclusion.

14. Separate systemic and local risk

Systemic dose per body mass is appropriate for many systemic endpoints. Local irritation or tissue injury can depend on amount per contact area, concentration, residence time, repeated contact and tissue susceptibility. A large systemic margin cannot compensate for an unacceptable local concentration. Surface-bound or particulate species may create local effects without appearing as freely dissolved extractables. ER-254 records this limitation and routes the physical or application-specific question to the relevant evidence stream.

15. Treat genotoxicity, carcinogenicity and reproduction explicitly

Review structural alerts, study reliability, exposure duration and mode of action. A negative general systemic-toxicity dataset does not close genotoxic or developmental concerns. Conversely, an alert is a signal for weight-of-evidence assessment, not automatic proof of harm. For incomplete identities, use the more conservative plausible structure or obtain analytical confirmation. High-consequence uncertainty should not be resolved by averaging.

16. Evaluate mixtures and aggregate exposure

Group constituents with common target organs, modes of action or structural alerts where evidence supports additivity. Consider aggregate exposure from multiple devices when foreseeable. Document why independent assessment is adequate if no mixture adjustment is used. Unknown features cannot be assigned zero toxicity. Their response, estimated quantity, class evidence and analytical uncertainty should drive targeted identification or conservative screening.

17. Use non-compensatory gates

Gate	Required evidence	Blocking failure
Identity	Confirmed or bounded chemical hypothesis	Hazard assignment remains uncertain
Device state	Clinically relevant process and ageing state	Exposure is not representative
Exposure	Quantity, frequency, route, duration and population	Risk cannot be quantified
Hazard	Endpoint-relevant point of departure and quality review	Tolerable exposure is unsupported
Extrapolation	Route, duration and population rationale	Derived limit is not transferable
Read-across	Structural, metabolic and toxicodynamic concordance	Analogue cannot carry the conclusion
Margin	Compatible numerator, denominator and uncertainty	Scalar result is uninterpretable
Exceptions	Genotoxic, local, mixture and cohort-of-concern review	General threshold cannot close risk

Evidence strength in one gate cannot average away failure of another. Unresolved gates require more chemistry, toxicology, process control, biological evidence or an explicit device risk decision.

18. Resolve discordance

When analytical exposure, in vitro response, in vivo evidence or clinical history disagree, first verify identity, device state, dose metric, route, duration and endpoint comparability. Examine whether the discrepancy reflects extraction severity, assay interference, metabolism, local concentration or batch variation. Record competing interpretations and select a discriminating next step. Do not retain only the most favourable line of evidence.

19. Control changes over the lifecycle

Trigger reassessment for changes in formulation, supplier, printer, exposure dose, wash, cure, sterilisation, packaging, shelf life, geometry, surface area, patient population, frequency of use, analytical identification or hazard information. Recalculate exposure and margin when any material input changes. New toxicology can invalidate an earlier limit even when manufacturing is unchanged. Conversely, better identification or bioavailability evidence may legitimately reduce uncertainty if its applicability is documented.

20. Minimum reporting set

Report assessor qualifications; device and process state; intended contact and population; constituent inventory and identity confidence; analytical source and uncertainty; exposure equations and assumptions; literature strategy; critical studies; point of departure; uncertainty and modifying factors; read-across justification; screening-threshold domain; endpoint-specific margins; mixture and local-risk analysis; unresolved gaps; decision and change triggers.

21. Knowledge boundary

The standards define the current constituent-risk framework [1-3], and FDA guidance situates it within risk-based device evaluation [4]. Case studies demonstrate how point-of-departure, extraction severity and route extrapolation affect conclusions [5,6]. A recent PBPK analysis informs uncertainty-factor refinement [7]. None establishes safety for an unspecified photopolymer formulation, device geometry or clinical use.

22. Limitations

References [1-4] were verified against current official records; references [5-7] were verified at detailed primary-record depth. Controlled standards and jurisdictional requirements govern implementation. This review does not provide legal advice, disclose proprietary composition, derive a product-specific tolerable intake or declare any device safe.

23. Conclusions

Constituent toxicological risk assessment is a chain of matched evidence: reliable identity, representative exposure, endpoint-relevant hazard data, justified extrapolation and transparent uncertainty. Read-across and screening thresholds are bounded tools, while margin of safety is an interpretable ratio only when its inputs match. A defensible conclusion preserves unknowns, local and high-consequence hazards, mixture considerations and lifecycle change triggers.

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