

Biological response in photopolymer additive manufacturing: a review of formulation chemistry, workflow variables and qualification constraints in dental and biomedical applications

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Statement of Significance

This review synthesises the published evidence on biological response in photopolymer additive manufacturing, focusing on how formulation chemistry, workflow execution, application context and temporal exposure interact to shape biocompatibility outcomes. Rather than treating photopolymer resins, post-processing conditions or device applications as isolated determinants, the review evaluates the evidence linking residual species, conversion behaviour, workflow variables, extractables, sterilisation and longitudinal service conditions. Recurrent limitations in standardised extractables methodology, workflow reporting, spatial conversion characterisation and long-term biological evaluation appear across the published literature. These observations define the current inferential boundaries of the field and support more evidence-consistent interpretation of biocompatibility data for additively manufactured dental and biomedical photopolymer devices.

Keywords: photopolymer, additive manufacturing, biocompatibility, biological response, dental polymers, orthodontic aligners, denture base, residual monomer, extractables, ISO 10993, ISO 20795-1, workflow validation

Abstract

Photopolymer vat photopolymerisation has expanded from prototyping into manufacturing and research workflows for dental and biomedical devices, including direct-printed clear orthodontic aligners, denture bases, surgical guides and research platforms. The regulatory environment has evolved in parallel through EU Medical Device Regulation 2017/745, revisions within the ISO 10993 series, and increased regulatory scrutiny of photopolymer constituents such as diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO). Against this backdrop, the term biocompatible resin continues to be used in ways that can conflate properties of a liquid formulation with the biological response of the cured printed device. The biological response of a printed device is not defined by formulation alone; it emerges from the interaction between formulation chemistry, photopolymerisation, post-processing, ageing under intended-use conditions and the chemical and mechanical environment of the device in service.

This review examines the hypothesis that biocompatibility in photopolymer additive manufacturing is more appropriately treated as an outcome of interacting engineering layers — formulation design, workflow control, extraction qualification and temporal stability — than as a property of the raw material. The hypothesis is examined against the peer-reviewed evidence base on residual species characterisation, post-cure degree of conversion, photoinitiator substitution, cytotoxicity assessment, hydrolytic and salivary stability and clinical performance of additively manufactured dental and medical devices. Two broad formulation approaches currently observed in the field — oligomer-dominant systems with reduced low-molecular-weight reactive fraction, and conventional monomer-based formulations with screened components and partial bio-derived content — are mapped against the application space, with the limitations of each approach made explicit. Standardised extractables methodology and longer-term clinical follow-up emerge as principal research priorities through 2030.

1. Introduction

1.1 Photopolymer additive manufacturing in medical and dental contexts

Photopolymer additive manufacturing has been increasingly applied to dental and biomedical devices over the past decade, with applications documented in the peer-reviewed literature including orthodontic clear aligners, denture bases, surgical guides and research-grade tissue-contact platforms. The common technical basis is the conversion of photo-reactive monomeric or oligomeric formulations into solid networks by controlled light exposure. Because the final cured state depends on both formulation and processing, biological evaluation of the finished article cannot be inferred from the liquid resin alone. [14,17,38,39,42]

1.2 The ambiguity of the term "biocompatible resin"

The published photopolymer literature, both academic and commercial, continues to use the term biocompatible resin in ways that conflate two technically distinct meanings. In one usage, the term refers to a liquid formulation whose constituent raw materials have been screened for known biological hazards. In the other usage, the term refers to a printed device that has passed cytotoxicity, sensitisation and irritation testing under ISO 10993 protocols within a specified intended use. These two meanings are not equivalent. The first refers to formulation-level properties of the liquid input; the second refers to system-level properties of the cured output produced by a specific printer, workflow and post-processing chain. The technical literature has documented cases in which photopolymer systems certified as biocompatible at the formulation level have produced printed devices with measurable cytotoxicity, ovotoxicity, or leaching of residual species exceeding the limits applicable to the intended use. These observations should not be read as failures of the certification system in itself, but as consequences of a more fundamental issue: the printed device is not the liquid resin, and biological response is determined by the cured network, the residual species trapped within it, the ageing behaviour of the cured polymer under intended use conditions, and the exposure environment of the device in service. Operational definitions for biocompatible, residual species, extractables, leachables, oligomer-dominant and adjacent terms are provided in section 2. [14,17,19,24,25,39]

1.3 The system-level reality of photopolymer biocompatibility

Photopolymer additive manufacturing is a multivariable process in which the cured material is not fully defined by the formulation alone. The final state of the polymer network depends on a chain of variables that interact non-linearly: the optical irradiance delivered to the resin by the specific printer, the layer thickness and exposure time, the build orientation and geometric thickness of the printed part, the washing protocol used to remove uncured surface resin, the light intensity and spectral matching of the post-curing apparatus, the optional thermal post-curing parameters, the storage and handling conditions, and the chemical, thermal and mechanical environment to which the device is exposed in service. [10,11,26,28,40]

Complete conversion of all polymerisable functionalities is not generally achieved under practical photopolymerisation conditions, and reported degree of conversion is strongly formulation- and workflow-dependent. Degree of conversion measures the fraction of polymerisable functionalities that has reacted; it is not, by itself, a direct mass measurement of free residual monomer. In systems containing monofunctional monomers, an unreacted functionality on such a molecule corresponds to residual monomer that has not been covalently incorporated into the polymer network. In multifunctional monomers and oligomers, however, unreacted functionalities can also remain as pendant groups on species that are already covalently incorporated. Residual monomer content and leachable-species concentrations therefore require independent chemical determination. The cured network may additionally contain mobile monomers, oligomeric species, photoinitiator or additive residues, photolysis products and other reaction by-products, whose biological relevance depends on chemical identity, mobility and exposure conditions. [10,11,18,20,37,40]

A further variable is the temporal evolution of the cured polymer under service conditions. Hydrolytic exposure, saliva, thermal cycling, sterilisation where applicable and mechanical loading can modify surface properties, mechanical performance and the release of chemical species over time. Studies on directly printed aligners have documented changes after intraoral use or artificial-saliva ageing, but the relationship between accelerated in vitro ageing and long-term clinical biological response remains incompletely established. The biological profile measured immediately after fabrication should therefore not be assumed to represent the complete service-life profile of the device. [16,18,31,32,35,44]

1.4 Formulation approaches and the limits of formulation-level design

The biocompatibility design space for photopolymer additive manufacturing currently supports two broad formulation approaches, both with established positions in commercial portfolios and in the peer-reviewed literature. The first approach favours oligomer-dominant reactive systems, in which the low-molecular-weight reactive fraction has been intentionally reduced relative to conventional photopolymer architectures, intending a reduced baseline of mobile residual species in the cured network. The second approach favours conventional monomer-based formulations with screened components and partial bio-derived content, applied where the mechanical or optical performance demanded by the application — direct-printed clear orthodontic aligners are the paradigm case — cannot be obtained within the first approach. Section 5 develops both approaches in technical detail and provides the operational definitions used throughout the review. [38,39]

Neither approach, in isolation, delivers a biocompatible device. The published evidence does not support reading either approach as a sufficient solution. No single formulation strategy currently eliminates the need for workflow validation, extraction testing and application-specific qualification. Oligomer-dominant systems may reduce specific classes of residual species but do not inherently guarantee device-level biological safety. Bio-derived components do not automatically deliver lower extractables or lower cytotoxicity than petroleum-derived equivalents. High degree of conversion is necessary but not sufficient — the chemical identity of the residual fraction, not only its absolute quantity, determines the leaching behaviour. In vitro cytotoxicity, while widely used as a screening tool, correlates imperfectly with in vivo outcomes and with clinical performance over the service life of the device. These tensions in the evidence base are addressed in subsequent sections; the present section establishes only that formulation-level design must be combined with workflow validation, extraction qualification and stability characterisation to translate a formulation- and workflow-control baseline into a device-level evaluation outcome. [11,14,17,18,24,25,37,39]

1.5 Scope, objectives and disclosure

This review covers the application of vat photopolymerisation — comprising stereolithography, digital light processing and liquid crystal display masked stereolithography — to medical and dental device manufacturing where biocompatibility considerations are central. Adjacent additive manufacturing technologies are referenced where they extend the engineering envelope but are not the primary subject of this review.

The objectives of the review are threefold: to organise the available evidence on photopolymer biocompatibility around the distinction between formulation-level properties of the liquid resin and system-level properties of the cured device under service conditions; to map the current formulation approaches against the application space they are intended to serve, including their respective limitations; and to identify the principal research priorities for the field through 2030. Section 2 defines the regulatory framework and operational terminology. Section 3 introduces failure modes of photopolymer biocompatibility and section 4 examines the published evidence for each. Section 5 develops formulation approaches; section 6 develops workflow control architecture and the temporal stability of the cured network. Section 7 maps the design space against application areas. Section 8 presents a comparative analysis, section 9 identifies open challenges through 2030, and section 10 summarises the limitations of the analysis presented.

This review is written from an industrial-academic position. The author is the founder and Scientific Director of Resyner Technologies S.L. / 3Dresyns, a manufacturer active in photopolymer materials for additive manufacturing. This affiliation is disclosed explicitly. Commercial materials are discussed only where they are represented in the cited published evidence and are not used as substitutes for peer-reviewed evidence.

2. Regulatory framework and operational definitions

2.1 Operational definitions and terminological ambiguity

The photopolymer additive manufacturing literature uses several terms whose technical content varies across sources, often with consequences for how empirical results are compared and how regulatory claims are interpreted. This section defines, for operational use in the remainder of this review, the meaning attached to each of the most consequential terms. [1,4,5,39]

Biocompatibility, in the operational sense used throughout this review, refers to the biological response of a finished printed device under defined intended-use conditions, evaluated according to the relevant ISO 10993 series of standards. The term is therefore reserved for system-level outcomes of the cured device in service, and is not used as a property of the liquid resin in isolation. Where authors of cited studies have used the term in the alternative sense — that is, applied to a liquid formulation whose constituent raw materials have been screened — this usage is preserved in the citation and clarified in the surrounding text where the distinction matters. [1]

Residual species, in the operational sense used here, refers to the umbrella population of low-molecular-weight species present in the cured polymer network after photopolymerisation and post-cure, comprising unreacted monomers, oligomer fragments, photoinitiator fragments and photolysis products, light-blocking additive species, pigment-related species and reaction by-products. Residual monomer is used in the narrower sense of the unreacted monomer fraction specifically, in particular where regulatory limits (such as ISO 20795-1) are quantitatively expressed as a residual monomer content. [11,18,37]

Extractables and leachables are used in the standard regulatory sense established by the ISO 10993-18:2020 framework and reinforced by the EU MDR Annex I Section 10.4: extractables are species that migrate from the cured device into a solvent under defined exaggerated extraction conditions; leachables are species that migrate from the cured device into the contact environment under intended-use conditions. The chemical identity of these species depends on the formulation, the photopolymerisation completeness, the post-processing chain and the contact medium. [4,49]

Oligomer-dominant systems, for the purposes of this review, refers operationally to formulations in which the majority of the reactive fraction is constituted by oligomeric or macromeric species and where the concentration of mobile low-molecular-weight reactive diluents has been intentionally reduced relative to conventional photopolymer architectures. The term is used here as an operational category to discuss formulation design choices and is not an established field classification with universally agreed quantitative thresholds. Practical formulation realities mean that oligomer-dominant systems may still contain measurable concentrations of low-molecular-weight reactive diluents introduced for viscosity control; the term denotes design intent and direction, not absolute monomer absence. [38,39]

Partially bio-based formulations, for the purposes of this review, refers to monomer-based reactive systems in which a fraction of the reactive components is derived from biological feedstocks rather than petroleum-derived feedstocks. The term is used descriptively to reflect the composition of certain commercial systems and does not, in itself, carry any implication about cytotoxicity, extractables behaviour or biological response of the cured device. As examined in section 5, bio-derived components do not automatically yield lower extractables or lower cytotoxicity than petroleum-derived equivalents. [22,23]

The terminological landscape of the field as a whole remains heterogeneous. Terms such as medical-grade, certified, non-toxic, ISO compliant, Class I and biocompatible are used in commercial and academic literature with overlapping and often inconsistent technical content. The framework adopted in this review treats these terms as descriptors of specific compliance acts at the formulation level, the device level or the manufacturing process level, and not as interchangeable descriptors of biological safety. The distinction matters because, as the evidence summarised in section 4 demonstrates, a formulation may satisfy several formulation-level descriptors and still produce a device that does not meet the corresponding device-level requirements under the intended-use exposure conditions. [39]

2.2 Regulatory distinction between raw material and finished device

The European Medical Device Regulation (Regulation EU 2017/745, MDR) became fully applicable on 26 May 2021, replacing the earlier Medical Device Directive 93/42/EEC. The regulation establishes a clear legal distinction between raw manufacturing materials and finished medical devices: raw materials are supplied with technical documentation and Instructions for Use, while the conformity assessment, biological evaluation, validation, CE marking, post-market surveillance and full regulatory responsibility for a finished device lie with the legal manufacturer of that device. A photopolymer resin, in this framework, is a raw manufacturing material. The finished device produced by additive manufacturing from that resin — whether a clear aligner, a denture base, a surgical guide or a microfluidic chip intended for clinical use — is the regulated medical device, defined by its intended medical use, final geometry, validated manufacturing process and applicable regulatory compliance. [2,8]

This distinction has direct chemistry implications for biocompatibility. Material-level data — whether toxicological screening of constituent monomers, formulation-level cytotoxicity testing of cured reference geometries, or ISO 10993 testing under defined reference configurations — are generated under specific processing conditions including a specific printer, exposure strategy, washing protocol and post-cure cycle. The same liquid resin processed under different parameters at the device manufacturer's facility may not reproduce the formulation-level biological response. The MDR therefore requires the device manufacturer to validate the full manufacturing workflow under its own conditions and to maintain the chain of evidence connecting raw material to finished device. [1,2,4]

2.3 Chemical characterisation and biological evaluation frameworks

ISO 10993-1:2025 sets requirements and general principles for evaluating biological safety within a risk-management process and aligns biological evaluation with the broader risk-management approach. ISO 10993-18 provides the framework for chemical characterisation of medical-device materials, while ISO 10993-12 addresses sample preparation and preparation of extracts for biological testing and can also be relevant to chemical-characterisation extraction procedures. These standards support a risk-based evaluation of the finished device rather than a stand-alone designation of the uncured resin. [1,4,49]

ISO 10993-18 establishes chemical-characterisation principles and requires extraction conditions to be selected and justified in relation to the device and the analytical question. Because residual species span a range of polarities, published studies use extraction media with different solvent characteristics; however, solvent identity, solvent ratio, temperature, duration, sample geometry and surface-to-volume ratio vary materially across studies. Specific solvent systems used in individual studies should therefore not be presented as a universal

ISO-mandated sequential extraction protocol. This methodological heterogeneity is a major limitation when comparing extractables and leachables data across additively manufactured photopolymers. [4,11,12,18,37,49]

For denture-base polymers, ISO 20795-1:2013 specifies material requirements and test methods. Peer-reviewed work applying the standard reports an upper limit of 2.2 mass% for residual methyl methacrylate in the relevant denture-base categories and identifies chromatographic methods, including HPLC, for determination of residual monomer content. The standard also specifies water-sorption and water-solubility requirements; recent work reported water-solubility values of 3.01 and 3.22 $\mu\text{g}/\text{mm}^3$ for two additively manufactured denture-base materials, above the 1.6 $\mu\text{g}/\text{mm}^3$ upper limit reported for the tested category. Residual monomer content and degree of conversion are distinct quantities and should not be compared as if they were the same endpoint. ISO 4049 applies to polymer-based restorative materials, while Quality-by-Design concepts have separately been discussed as a framework for medical-device development. [5,6,9,13,34]

2.4 Limitations of current validation paradigms

Three structural limitations of the current validation paradigm are relevant for the framework developed in this review. First, biocompatibility-related data generated under defined reference configurations cannot be universally extrapolated across workflows. Changes in printer technology, exposure strategy, build orientation, washing chemistry, post-cure protocol or sterilisation cycle may alter the cured polymer state and the extractables profile, requiring re-qualification at the device manufacturer level. This is a regulatory requirement but also a chemistry constraint: the cured network produced by a specific processing chain is not equivalent to the cured network produced by a different chain from the same liquid resin. [1,2,4,29,39]

Second, the standardisation of extractables methodology for additively manufactured devices remains incomplete. ISO 10993-18 specifies extraction principles, but the application to additively manufactured geometries — with their layer-wise internal structure, build-orientation-dependent surface chemistry and complex internal accessibility — has not been systematised across the field. Comparison between published extractables studies is therefore limited by methodological heterogeneity: different solvents, different extraction temperatures, different extraction durations, different surface-to-volume ratios and different reporting conventions are observed in the literature. [4,37,39]

Third, the validation paradigm has historically emphasised cross-sectional cytotoxicity testing at the point of device fabrication. As section 1.3 has established and as the longitudinal evidence summarised in section 4 documents, the biocompatibility profile of an additively manufactured device evolves under intended-use conditions over weeks to months of intraoral exposure, hydrolytic interaction, mechanical loading and sterilisation cycles where applicable. The ISO 10993-1:2025 lifecycle reframing partially addresses this gap, but the integration of long-term clinical follow-up data into routine biological evaluation of additively manufactured devices is not yet established practice. [1,14,17,31,32,35]

3. Three failure modes of photopolymer biocompatibility

The conceptual architecture of the present review identifies three failure modes through which photopolymer additive manufacturing of medical and dental devices may yield outcomes that do not meet device-level biocompatibility requirements under the relevant ISO 10993 framework. The three failure modes are not mutually exclusive and are frequently observed in combination; they are presented separately because each implicates a distinct set of engineering controls, evidentiary requirements and validation activities. Section 4 summarises the peer-reviewed evidence for each.

3.1 Failure mode 1 - Formulation-level hazard

The first failure mode arises from constituent species whose toxicological profile or potential release is incompatible with the intended use of the finished device. TPO was added to the REACH Candidate List as a substance of very high concern on the basis of reproductive toxicity and, in November 2025, ECHA recommended it for inclusion in Annex XIV. At the time of this revision, the ECHA recommendation page does not show a date of inclusion in the Authorisation List. The regulatory development therefore creates substantial substitution and risk-management pressure but should not be described as a blanket legal requirement that all European photopolymer applications have already eliminated TPO. Comparative work on TPO, TPO-L and BAPO also shows that substitution of a photoinitiator requires independent evaluation of the resulting formulation rather than an assumption of improved biological performance. [3,7,20]

Beyond photoinitiators, formulation-level hazard can arise from reactive diluents, monomers, additives, stabilisers, pigments and photolysis or reaction products. The relevant question is not whether a constituent belongs to a broad chemical family but whether the constituent and its transformation products create an unacceptable exposure under the intended use of the finished device. Constituent screening therefore needs to be connected to chemical characterisation of the cured article and to the biological endpoints required for that use. [14,17,24,39]

3.2 Failure mode 2 - Workflow execution gap

A second failure mode arises when processing produces a cured state different from the state assumed during qualification. Conversion is influenced by delivered light dose, spectral match, layer thickness, geometry, oxygen inhibition, molecular mobility as the network forms and post-cure conditions. The final material is therefore better treated as a workflow-dependent polymer network than as a chemically invariant consequence of the liquid formulation. [10,11,26,28,40]

Katheng and colleagues evaluated Formlabs Clear resin processed with a Form 2 printer, Form Wash and Form Cure under several post-polymerisation time and temperature combinations and reported degree-of-polymerisation values in the approximately 70-90% range for that specific material and workflow. These data demonstrate incomplete conversion under the conditions tested, but they do not establish a universal upper limit for dental SLA systems. More recent work on other chemistries has reported substantially higher conversion values. Most importantly, the complement of degree of conversion cannot be equated directly with residual monomer mass content: in monofunctional systems an unreacted functionality corresponds to an unincorporated residual monomer molecule, whereas in multifunctional systems unreacted functionalities can also be pendant groups on network-bound species. Residual monomer therefore requires independent analytical determination. [10,11,40]

The workflow-execution concept should not be read as implying that qualified photopolymer workflows are intrinsically inadequate. Rather, the evidence shows that conversion, leaching, cytotoxicity and mechanical outcomes are sensitive to material- and process-specific conditions. The relevant qualification question is whether the defined workflow produces a finished device that meets the requirements associated with its intended use. [14,17,24]

Light attenuation deserves particular attention in pigmented, coloured, opaque or thick-section geometries. Absorbing species used to control optical penetration during printing can also attenuate post-cure light. The magnitude of any through-thickness conversion gradient depends on formulation, absorption spectrum, geometry, cure wavelength and exposure history. Published quantitative characterisation of these gradients remains limited, so numerical claims about internal residual-monomer fractions or biological-response gradients should not be generalised without direct measurements for the specific formulation-geometry-workflow combination. [38,40]

Thermal post-curing can increase conversion in some formulations by increasing molecular mobility and enabling further reaction in regions that receive limited additional light. Nitrogen or other oxygen-reduced post-curing can also improve surface conversion for some systems. Whether thermal treatment, an inert atmosphere or a combined protocol is required, and the appropriate time and temperature, are formulation- and geometry-specific and should be stated only where supported by the relevant study or manufacturer-qualified workflow. [10,28,29,40]

Additional workflow variables include removal of uncured surface resin, condition of the washing solvent and oxygen inhibition at exposed surfaces. Flierl et al. found no significant dimensional deviations at 0-10 wt% dissolved-resin contamination in the tested rinsing medium, while higher contamination produced increasing dimensional effects, particularly at 20-30 wt% depending on feature geometry. That study addressed dimensional stability and should not be used as direct evidence for an extractables-removal threshold. Separate studies show that washing solvent and post-curing conditions can alter cytotoxicity outcomes, and nitrogen post-curing can improve conversion and cytocompatibility in some materials. [26,27,28]

3.3 Failure mode 3 — Temporal instability and extraction behaviour The third failure mode arises when a device acceptably manufactured under failure-mode-1 and failure-mode-2 controls nonetheless yields a biological response under intended-use conditions that diverges from the response observed at the point of fabrication. Two coupled mechanisms contribute.

Post-curing increases conversion but is not equivalent to quantitative extraction of all potentially releasable species. Chemical characterisation therefore needs extraction conditions appropriate to the analytical question and the device. ISO 10993-12 and ISO 10993-18 provide requirements and guidance for sample preparation and chemical characterisation, while published dental studies illustrate that solvent choice materially affects the species and quantities detected. No single solvent or universal solvent sequence should be assumed to recover the entire chemically heterogeneous residual-species population. [4,11,12,18,37,49]

The chemical identity of the residual or leachable fraction matters in addition to its quantity. Berghaus et al. reported that degree of conversion did not correlate directly with residual-monomer elution across the materials they tested, and aligner studies likewise show that release profiles depend on chemistry and ageing conditions. Degree of conversion is therefore useful as a network-state descriptor but not as a stand-alone surrogate for leachable exposure or biological response. [11,12,18,37]

Soxhlet extraction has been evaluated as an intensive solvent-extraction approach for reducing leachable cytotoxicity from printed photopolymers. In a comparative study by Rengarajan et al., Soxhlet extraction reduced measured leachable cytotoxicity more effectively than additional curing or passivation for the polymers tested. This supports its value as an analytical or research method for specific materials, but it does not establish a universal asymptotic extraction limit for all cured photopolymer networks or prove equivalence with long-term clinical exposure. [36]

The second mechanism is temporal evolution of the cured polymer during use. Intraoral and artificial-saliva studies have documented changes in surface state, mechanical properties, optical behaviour and chemical release over time. Chen et al. used a 45-day artificial-saliva protocol as an accelerated ageing condition and described it as approximating a longer service interval for the surface-property model; such accelerated protocols should not be interpreted as a universally validated one-to-one conversion to clinical years. Long-term biological response therefore remains less well characterised than short-term in vitro endpoints. [16,31,32,35,44]

Engineering objective and bridge to subsequent sections

The three failure modes are mutually addressable through coordinated engineering control. The corresponding engineering objective is to reach the maximum achievable degree of conversion under controlled conditions, to minimise the formation and retention of biologically problematic residual species, to reduce extractables and leachables to levels acceptable for the intended use, and to validate the full manufacturing workflow at device level rather than only at reference-coupon level. Section 6 develops the operational architecture for achieving this objective; section 7 maps the architecture against the application space.

4. Published evidence base

This section summarises the peer-reviewed evidence base on photopolymer additive manufacturing biocompatibility outcomes, organised around the categories of evidence rather than around the conceptual failure modes of section 3. The selection is illustrative rather than exhaustive; representative studies are chosen to document the principal observations across the field. Three caveats apply throughout. First, the studies cited adopt heterogeneous extraction protocols, cell models, exposure conditions, photopolymer chemistries and reporting conventions, which limits direct cross-study comparison; the discussion focuses on the qualitative patterns rather than on quantitative aggregation. Second, the inclusion of a study showing acceptable biological response under one set of conditions does not imply universal safety of the system under all conditions, and the inclusion of a study showing problematic response does not imply universal failure. Third, where contradictory findings exist across the literature, both are reported, and an attempt is made to identify the methodological or experimental differences that may underlie the divergence.

4.1 Residual species and extractables evidence

The published evidence on the residual species composition of cured photopolymer additive manufacturing materials covers two main analytical approaches: spectroscopic determination of the degree of conversion (typically Fourier transform infrared spectroscopy, occasionally Raman or differential scanning calorimetry), and chromatographic determination of leachable species concentrations in extraction media (typically high-performance liquid chromatography coupled to ultraviolet or mass spectrometric detection, occasionally gas chromatography-mass spectrometry). [11,12,13,18,37,40]

Berghaus and colleagues compared three-dimensionally printed, milled and self-cured resin-based composite materials under matched extraction conditions. They found measurable residual-monomer elution in organic extraction media and reported that degree of conversion did not predict residual-monomer release across the compared materials. The result supports treating network structure, chemical identity and extraction conditions as additional determinants of leaching rather than using degree of conversion alone. [11]

Bouchema and colleagues compared three direct-print aligner resins under defined post-curing and ageing conditions and documented material-dependent leaching and biological responses. The study reinforces that ageing, formulation chemistry and post-processing jointly shape the observed extractables and cytotoxicity profile; the findings should not be extrapolated to all direct-print aligner resins without material-specific evidence. [12]

For denture-base materials, Vuksic et al. measured residual monomer content by HPLC under ISO 20795-1-aligned conditions and reported values spanning roughly 0.05 to 3.2 mass% across different manufacturing routes. In a separate study, the same group reported water-solubility values of 3.01 and 3.22 $\mu\text{g}/\text{mm}^3$ for two additively manufactured denture-base materials, above the 1.6 $\mu\text{g}/\text{mm}^3$ limit applied in that investigation. These endpoints should be interpreted separately: residual monomer content is not degree of conversion, and water solubility represents a broader mass-loss endpoint rather than a monomer-specific measurement. [13,34]

Across studies, residual-species characterisation depends strongly on the manufacturing workflow, extraction medium, extraction time and temperature, sample geometry and analytical method. Reviews of monomer-release methodology document substantial heterogeneity in study design, which limits direct quantitative comparison between materials and laboratories. [37]

4.2 Cytotoxicity and biological response evidence

Published biological-response studies use a range of cell systems and endpoints, including human gingival fibroblasts, mesenchymal stromal cells and reproductive-toxicity models. Results differ by material, extraction conditions, surface treatment and post-processing. These differences make it inappropriate to infer a universal biological response from the label applied to a liquid resin or from a single in vitro endpoint. [14,17,19,24,25,43]

Rogers et al. reported ovo-toxic leachate release from two Formlabs SLA dental resins evaluated under manufacturer-recommended workflows. Oxygen-plasma surface treatment attenuated the observed toxicity for one material but not the other, and Tinuvin 292 was identified as a major ovo-toxic component of one leachate. Separately, Alt et al. reported impaired adhesion and proliferation of human mesenchymal stromal cells after indirect exposure to a Class I biocompatible DLP-printed acrylate. These studies illustrate that device-level biological response can remain sensitive to material composition and post-processing even when a material carries a biocompatibility-related designation. [19,25]

Other studies report acceptable in vitro cytocompatibility under defined workflows. Brooks and Yadavalli showed that post-print processing strongly affected cell viability for several printed photopolymers, and Wezgowiec et al. reported material- and fabrication-dependent differences across intraoral appliance materials. Campobasso et al. likewise demonstrated that post-curing procedure can influence the cytotoxicity measured for a directly printed aligner material. These findings support workflow-specific interpretation rather than a binary classification of resin chemistries. [22,24,43]

The apparent contradictions in the cytotoxicity literature largely reflect differences in material chemistry, specimen preparation, extraction conditions, cell model, exposure duration and post-processing. A material can therefore yield different in vitro outcomes under different test configurations without those studies necessarily being mutually inconsistent. [14,17,24,25,43]

The implication is twofold. First, a formulation-level designation does not directly predict biological response for every printed geometry and workflow. Second, in vitro cytotoxicity is a screening endpoint within a broader biological-evaluation process and should not be treated as a complete predictor of long-term clinical performance. [14,17]

4.3 Workflow-dependent variability

The evidence on workflow-dependent variability in photopolymer additive manufacturing biocompatibility outcomes covers six main process variables: printer architecture and ultraviolet irradiance, build orientation and layer thickness, washing protocol and solvent management, light post-cure parameters, thermal post-cure parameters, and oxygen exclusion during post-cure. [10,15,22,26,27,28,29,30,40,43]

Katheng et al. demonstrated that post-polymerisation time and temperature affected the degree of polymerisation and dimensional accuracy of a specific SLA dental resin. The study is useful evidence for workflow sensitivity but should not be read as establishing a universal conversion range for all dental photopolymers. [10]

Washing and rinsing can alter biological and dimensional outcomes. Brooks and Yadavalli showed substantial post-processing effects on leachable cytotoxicity; Lopez-Garcia et al. compared rinsing solvents and curing units for a dental 3D-printed resin; and Flierl et al. quantified dimensional effects associated with increasing dissolved-resin contamination of the rinsing medium. Together, these studies show that washing is a controlled process variable, but they do not support a single universal solvent, duration or contamination threshold for all resins. [22,26,27]

Post-curing is likewise material-specific. Studies show effects of temperature, atmosphere and photoinitiator system on conversion, cytotoxicity and mechanical properties. Light, heat and inert-atmosphere strategies should therefore be described as formulation-dependent processing options rather than as universal requirements for transparent, pigmented or thick-section parts. [10,20,28,29,40]

Oxygen exclusion during post-curing can be consequential for some formulations. Gladrow et al. reported higher degree of conversion and improved cytocompatibility for a 3D-printed denture-base resin post-cured under nitrogen, while Simunovic et al. reported high

conversion in a polyurethane aligner system and a measurable influence of polymerisation environment. These results support material-specific control of post-curing atmosphere without implying that nitrogen is required for every medical or dental photopolymer. [28,40]

4.4 Temporal and ageing evidence

Longitudinal evidence remains more limited than point-of-fabrication characterisation. Available studies include intraoral ageing of directly printed aligners, artificial-saliva ageing, clinical-use comparisons and sterilisation studies. These studies collectively show that properties can evolve after fabrication, but they examine different endpoints and timescales and should not be collapsed into a single quantitative ageing model. [16,31,32,35,44]

Sayahpour et al. prospectively evaluated mechanical properties of directly printed and thermoformed aligners after intraoral ageing and documented material-dependent changes. The study provides in vivo evidence that service exposure can modify mechanical behaviour, while not by itself establishing a complete long-term biological-response profile. [31]

For denture-base materials, the strongest evidence in the present reference set concerns residual monomer content and water sorption or solubility measured under standardised laboratory conditions rather than multi-year longitudinal biological follow-up. This distinction is important: laboratory chemical endpoints can identify potential concerns but do not directly establish the clinical biological consequence over the service life of a denture. [13,34]

Across aligner and denture evidence, the defensible conclusion is that post-fabrication exposure can alter measured chemical, surface, optical or mechanical properties. The magnitude, direction and biological significance of those changes remain material- and protocol-dependent, and long-term clinical studies integrating chemical and biological endpoints remain comparatively sparse. [16,31,32,35,44]

4.5 Counterevidence and unresolved contradictions

Three substantive contradictions in the published evidence base are worth documenting explicitly, as they constrain the conclusions that can be drawn from the literature taken together.

The first contradiction is the conversion-leaching decorrelation. Berghaus et al. reported that degree of conversion did not correlate with residual-monomer elution, and aligner studies show that chemical release can evolve with ageing even when nominal conversion is high. These observations support measuring both network conversion and released species rather than substituting one endpoint for the other. [11,12,18]

The second ambiguity concerns formulation labels such as monomer-free, monomer-reduced or oligomer-dominant. Such labels can describe formulation intent but do not by themselves establish the extractables profile or biological response of the cured device. Published reviews of marketed resins likewise show inconsistent detail in composition, intended use and post-processing documentation. [17,39]

The third ambiguity concerns bio-derived chemistry. Experimental bio-based photopolymers demonstrate that biological response depends on the specific molecular structure and workflow rather than on renewable feedstock origin alone. Bio-derived content can be a legitimate formulation or sustainability attribute, but it is not a substitute for chemical characterisation and biological evaluation. [22,23]

The three contradictions documented here are not failures of the published literature; they are features of an evidence base in which the principal determinants of the biological response are interactive (formulation $\times$ workflow $\times$ geometry $\times$ time) rather than additive. Taken together, the published evidence supports interpreting the biological response of additively manufactured photopolymer devices as dependent on interacting formulation, workflow, geometric and temporal variables rather than on any single material descriptor in isolation. The methodological heterogeneity that underlies the documented contradictions is not resolved here; the standardisation priorities required to reduce this heterogeneity over the coming decade are identified in section 9.

5. Formulation approaches

The formulation design space for photopolymer additive manufacturing of medical and dental devices is multidimensional. Conversion completeness, viscosity, optical behaviour, mechanical properties, extractables profile, hydrolytic ageing, manufacturability and regulatory simplicity each impose constraints on the formulation, and no architecture optimises all of them simultaneously. This section describes five formulation approaches currently observed in the field, each occupying a different region of this design space. The approaches are presented descriptively, with chemistry rationale, accepted constraints, applications matched to those constraints, and the trade-offs accepted; the comparative synthesis in section 5.6 examines the design space as a whole. Throughout, the term biological outcome refers to demonstrated experimental or clinical observations rather than to inferences from formulation features alone. [38,39]

5.1 Conventional monomer-rich architectures

Conventional monomer-rich photopolymer formulations occupy a region of the design space characterised by reactive systems in which a substantial fraction of the polymerisable component is constituted by low-molecular-weight reactive diluent monomers and dimethacrylate monomers, photoinitiated by a Type I photoinitiator absorbing in the near-ultraviolet to visible range. The principal dimethacrylate chemistries documented in the dental and biomedical literature include the bisphenol-A-derived dimethacrylates (Bis-GMA, Bis-EMA), the urethane dimethacrylates (UDMA and its derivatives) and the triethylene glycol dimethacrylates (TEGDMA), with monofunctional reactive diluents such as hydroxyethyl methacrylate (HEMA) employed to reduce viscosity to processable levels. [38]

The processing constraints of this region are well characterised. The low-molecular-weight reactive fraction can reduce viscosity and support recoating and feature formation, but the biological interpretation of incomplete conversion requires care. For a monofunctional reactive diluent, a molecule whose sole polymerisable functionality remains unreacted is residual unincorporated monomer. For multifunctional dimethacrylates and oligomers, by contrast, unreacted double bonds can also remain as pendant functionalities on species already incorporated into the network. Degree of conversion therefore cannot be converted directly into a mass percentage of residual free monomer. Actual residual-monomer and leachable-species concentrations must be determined independently and depend on formulation chemistry and workflow. [11,38]

This region is matched to applications where low viscosity, high resolution, dimensional fidelity and clear optical transparency are dominant design constraints, and where the workflow is sufficiently controlled to manage the residual species fraction at the device level. Direct-printed clear orthodontic aligners are the paradigm case: the combination of mechanical toughness, foldability, dimensional fidelity and clear optical performance demanded by the application is currently achieved most reliably within this region of the design space. The trade-off accepted is the elevated baseline residual reactive fraction in the cured network, which displaces the burden of biocompatibility validation onto workflow control (washing, post-cure parameters, optional thermal post-cure) and onto extraction qualification rather than onto formulation-level reduction of mobile species. [17,42]

5.2 Oligomer-dominant architectures

Oligomer-dominant photopolymer formulations occupy a region of the design space characterised by reactive systems in which the majority of the reactive fraction is constituted by oligomeric or macromeric species — typically urethane-acrylate or urethane-methacrylate oligomers of intermediate-to-high molecular weight — and in which the concentration of mobile low-molecular-weight reactive diluents has been intentionally reduced relative to conventional monomer-rich architectures. As established in section 2.1, the term refers operationally to a formulation design direction within this review, not to an established field classification with universally agreed quantitative thresholds; practical formulations in this region may still contain measurable diluent fractions introduced for viscosity control. [39]

The processing constraints of this region differ from those of the monomer-rich region. The higher intrinsic viscosity associated with reduced low-MW reactive fraction narrows the processing envelope for high-throughput printing, particularly for layer recoating and for support of fine geometric features at the lower end of the resolution range. Cure depth is constrained by the reduced mobility of the larger reactive species during free-radical chain growth, with the network forming at lower conversion than would be achieved by an equivalent monomer-rich system under identical post-cure conditions if the post-cure parameters were not adjusted to compensate. Thermal post-cure becomes particularly relevant in this region for completion of network formation. The biological consequences of this design choice are less directly documented in the published literature, in part because comparative head-to-head studies controlling for workflow variables are limited. [38,39]

This region is matched to applications where the reduction of mobile low-molecular-weight reactive species is biologically relevant to the intended use, where viscosity tolerance of the workflow is high, and where the geometric features do not require sub-100-micron resolution. Rigid biocompatible surgical guides, dental restorative geometries in the higher-Shore range, and certain denture-base frameworks have been documented as falling within this matching. The trade-off accepted is the constrained processing envelope and the reduced flexibility for formulating across the full Shore hardness range with single-component oligomeric chemistry; lower-Shore flexible applications may require additional reactive diluent reintroduction to achieve the target mechanical behaviour, partly offsetting the formulation design intent. [39]

5.3 Bio-derived and partially bio-based systems

Bio-derived photopolymers include experimental soybean-oil-derived acrylates, vinyl-carbonate systems and other formulations in which part of the reactive chemistry originates from renewable feedstocks. These examples demonstrate a broad chemistry space rather than a single material class. Bio-derived content should therefore be treated as a compositional descriptor, not as evidence of lower cytotoxicity or lower leachable burden. [22,23]

Processing behaviour of bio-derived systems is chemistry-specific. Brooks and Yadavalli showed that post-processing materially affected cytotoxicity across different resin chemistries, while Russmueller et al. demonstrated a vinyl-carbonate biophotopolymer platform with a distinct in vivo and in vitro evaluation profile. The available evidence does not support a general rule that renewable feedstock origin predicts conversion, viscosity or biological response. [22,23]

The appropriate qualification approach for a bio-derived photopolymer is therefore the same risk-based approach applied to other reactive systems: characterise the formulation and cured network, control the manufacturing workflow, measure relevant extractables or leachables where required, and evaluate biological endpoints in relation to intended use. [22,23]

5.4 Photoinitiator strategies and the TPO regulatory transition

TPO has been subject to increasing EU regulatory scrutiny following its identification as a substance of very high concern for reproductive toxicity and ECHA's subsequent recommendation for inclusion in Annex XIV. This development is relevant to formulation strategy, but it should not be described as proof that every European photopolymer application is already legally required to use a TPO-free formulation. [3,7,20]

Alternative photoinitiator systems have different absorption spectra, efficiencies and biological profiles. Kim et al. directly compared TPO, TPO-L and BAPO in a 3D-printing resin and found differences in cytotoxicity, colour stability and dimensional accuracy. Such evidence supports formulation-specific comparison of alternatives rather than a presumption that replacing TPO automatically improves the biological profile. [20]

The practical consequence is that photoinitiator substitution requires re-evaluation of the integrated formulation and workflow, including spectral compatibility with the printer and post-cure source. The regulatory status of a constituent and the biological performance of the finished device are related but distinct questions. [3,20]

5.5 Pigments, absorbers and optical-control systems

Pigments, dyes and absorbers can influence optical penetration during printing and post-curing. Their effects depend on absorption spectrum, concentration, layer thickness, geometry and the spectral output of the curing system. These variables can affect print resolution and conversion depth and therefore belong within formulation- and workflow-specific qualification. [38]

Absorbing components can attenuate post-cure light through the printed thickness. The resulting conversion profile should be characterised where it is relevant to device performance, but the literature does not support a universal numerical conversion gradient or a universal thermal-post-cure temperature range across all pigmented dental photopolymers. Claims about internal conversion or residual species therefore need direct evidence for the specific material and geometry. [29,38,40]

Colorants and optical additives used in a medical or dental device should be included in device-level chemical characterisation and toxicological risk assessment as applicable to the intended use. Terms such as food-grade or biomedical-grade should not be used as generic substitutes for that evaluation unless a specific regulatory or compositional basis is documented. [28,29,38,40]

5.6 Comparative synthesis and unresolved trade-offs

The five regions of the formulation design space described in sections 5.1-5.5 are not steps along an evolutionary trajectory toward a future universal architecture; they are coexisting formulation approaches matched to different combinations of constraints. The conventional monomer-rich region preserves processing fluidity and optical clarity at the cost of elevated residual species inventory. The oligomer-dominant region reduces the mobile low-MW reactive fraction at the cost of viscosity and processing envelope. The bio-derived region offers compositional features whose biological consequences are chemistry-specific rather than category-general. The post-TPO photoinitiator region is itself a heterogeneous response to a regulatory event, with multiple alternatives offering different trade-offs in cytotoxicity, polymerisation efficiency and equipment compatibility. The pigmented and optical-control region enables geometric resolution and aesthetic outcomes at the cost of post-cure complexity and additive-level qualification requirements. [20,22,23,38,39]

No architecture simultaneously optimises conversion completeness, viscosity, optical control, mechanical flexibility, residual species reduction, hydrolytic stability, manufacturability and regulatory simplicity. The five tensions documented in the chemistry-comparative analysis above — mobility versus viscosity, cure depth versus optical control, extractables versus manufacturability, flexibility versus network density, conversion versus ageing behaviour — are not failures of formulation engineering; they are structural features of a multidimensional design space in which different design objectives are partially incompatible. [11,18,22,40]

The published evidence is consistent with the interpretation that different applications occupy different local optima in this design space rather than converging toward a single optimum. Direct-printed clear aligners operate at a local optimum where monomer functionality is required by the mechanical and optical performance envelope and where workflow control and extraction qualification carry the biocompatibility burden. Rigid biocompatible surgical guides operate at a different local optimum where mobile reactive species reduction is biologically relevant and where viscosity tolerance enables oligomer-dominant chemistry. Coloured dental restoratives operate at a local optimum requiring thermal post-cure validation. Each local optimum is defined by the constraints of its application rather than by a universal hierarchy of architectures. [17,39,42]

The question for the field is therefore not which formulation architecture is superior, but which trade-off position in the design space best matches the constraints of a given application, and how workflow control translates that formulation choice into device-level biological outcome. The coexistence of multiple formulation regions in current commercial portfolios is therefore an expected consequence of the multidimensional design space, not a sign of immaturity of the field; the consolidation pressure on the field is toward methodological standardisation of biological evaluation across the design space, not toward convergence on a single chemistry. [38,39]

6. Workflow control practices

The biological outcome of an additively manufactured photopolymer device depends on the cumulative result of multiple processing steps, each of which compensates one or more constraints introduced by the formulation, the geometry or the equipment, and each of which has documented operating envelopes within which it functions and failure boundaries beyond which it does not. This section reviews the workflow control practices documented in the literature, organised by the constraint each practice compensates. The practices described are application-dependent, formulation-dependent and geometry-dependent; the section does not propose a universal workflow architecture, and the practices are not presented as best-practice recommendations. The closing subsection examines the implications of workflow dependence for the interpretation of formulation-level biocompatibility claims. [10,22,26,28,29,40]

6.1 Pre-print qualification practices

Before printing, traceability of material batch, equipment condition and the applicable manufacturer instructions contributes to reproducibility. Calibration of printer and post-cure equipment is part of process control, but the published biological-response literature often reports these pre-print controls incompletely. This limits reconstruction of the exact workflow when studies are compared retrospectively. [14,17,29,39]

The evidence therefore supports documenting the material, printer, exposure settings, washing procedure, post-cure equipment and relevant storage or sterilisation conditions used to produce test specimens. It does not support a universal requirement for a particular incoming-inspection scheme or calibration interval across all photopolymer devices. [14,17,29,39]

6.2 Cure parameter practices

Exposure time, delivered irradiance, layer thickness, wavelength and build orientation can affect conversion, accuracy and mechanical properties. These parameters are specific to the resin-printer combination and should be reported when biological or chemical outcomes are compared. [10,29,38,40]

The literature supports material- and printer-specific parameter optimisation rather than a single exposure window transferable across systems. In particular, differences in photoinitiator absorption and optical attenuation can change the relationship between nominal printer settings and the cured network state. [10,20,29,40]

6.3 Washing and rinsing practices

Washing removes uncured or partially cured surface resin and can influence cytotoxicity, surface condition and dimensional accuracy. Published studies use different solvents, devices and contact times, and the optimal procedure is material-specific. [22,26,27,29]

Flierl et al. showed that dissolved-resin contamination of a rinsing medium can affect dimensional stability at higher contamination levels, while Lopez-Garcia et al. and Brooks and Yadavalli demonstrate that different post-processing choices can alter measured biological outcomes. These studies do not define a universal extractables-removal threshold for wash-solvent contamination. [22,26,27]

6.4 Post-cure practices

Post-curing is used to increase conversion and stabilise the printed network. Published studies demonstrate effects of time, temperature, curing atmosphere and photoinitiator system, but the magnitude and direction of those effects differ by material. [10,20,28,29,40]

Consequently, light-only, light-plus-heat and inert-atmosphere protocols should be treated as system-specific processing strategies. The relevant protocol is the one qualified for the material, geometry and intended use, not a generic rule based solely on whether a part is transparent, pigmented or thick. [10,20,28,29,40]

6.5 Downstream extraction and chemical characterisation

Where chemical characterisation requires extraction of potentially releasable species, the extraction design should be justified in relation to the device and analytical question. Published studies use static extraction, different solvent systems and, in some research settings, intensive approaches such as Soxhlet extraction. [4,11,12,18,36,37,49]

Soxhlet extraction can be useful for research or comparative detoxification of specific printed polymers, but it should not be presented as a universal manufacturing step or as proof that all clinically relevant leachables have been removed. The relationship between exhaustive laboratory extraction and long-term in-use release remains insufficiently characterised. [36,37]

6.6 Device-level quality control practices

Degree of conversion, residual monomer, extractables, mechanical properties and dimensional accuracy are distinct qualification endpoints. Spectroscopic methods such as FTIR or Raman are valuable for characterising conversion, while chromatographic methods are needed for analyte-specific residual-monomer or leachables measurements. [10,11,13,37,40]

The literature does not support a universal requirement to perform FTIR, Raman or destructive chemical analysis on every manufacturing batch or every device. Appropriate production controls depend on the validated process, risk analysis and applicable regulatory requirements. Analytical qualification measurements should therefore be distinguished from routine production quality-control methods. [10,11,13,37,40]

6.7 Workflow dependence and its consequence for formulation-level claims

The central evidence-supported observation is that formulation and workflow are coupled. A change in printer, exposure, washing, post-cure, sterilisation or storage can change the final network state and therefore may change chemical or biological outcomes. [10,22,26,28,29,40]

A resin shown to meet a biological endpoint under one defined workflow should not automatically be assumed to give the same result under a materially different workflow. Conversely, a problematic result obtained under one processing condition should not be generalised to every possible workflow for that formulation. [14,17,24,39]

For reporting and qualification, the defensible unit of interpretation is therefore the finished device produced by a defined manufacturing process and intended for a defined use. This framing is consistent with the risk-based logic of the ISO 10993 series and the MDR rather than with an intrinsic safe-or-unsafe label applied to the uncured resin. [1,2,4,39]

7. Application-specific qualification burdens

The formulation approaches and workflow control practices documented in sections 5 and 6 translate into different qualification burdens across the application space. The constraints that dominate the biological response, the workflow dependencies that become critical, the relative maturity of the available evidence and the principal unresolved uncertainties all vary substantially across applications. This section maps these variations across five application contexts and concludes with a synthesis of evidence gaps that recur across the application space. The intent is to compare qualification environments rather than product categories; the same formulation chemistry may operate within different qualification environments depending on the intended use.

7.1 Dental and orthodontic intraoral devices

Intraoral devices are exposed to saliva, temperature changes, mechanical loading and microbial colonisation. For directly printed aligners, available evidence includes leaching studies, short-term cytotoxicity, artificial-saliva ageing and prospective in vivo mechanical evaluations. The evidence base is growing but remains heterogeneous in material, workflow and endpoint. [14,17,18,31,32,35,42,44]

Washing, post-curing and surface state can influence biological outcomes. Bieger et al. reported surface-treatment-dependent fibroblast behaviour for printed occlusal-device materials, and aligner studies document leaching and ageing-related changes under defined conditions. Cleaning protocols must also preserve optical and mechanical performance, so processing choices should be justified for the specific material rather than generalised across all aligner resins. [15,18,22,26,32]

Short-term cytotoxicity and mechanical characterisation are better represented in the literature than long-term clinical biological response. Clinical-use and artificial-saliva studies provide important longitudinal information, but they do not yet establish a complete multi-month or multi-year exposure-response model for directly printed aligners. [14,17,31,32,35,42,44]

Key uncertainties include the correspondence between accelerated artificial-saliva ageing and clinical service, the in vivo significance of concentrations measured under laboratory extraction conditions, and the interaction between surface ageing, leaching and microbial colonisation. These are evidence limitations rather than properties that can be assigned to all aligner chemistries. [17,32,42,44]

7.2 Denture base and prosthodontic devices

Denture bases combine prolonged oral contact with material-specific requirements under ISO 20795-1. For the residual-monomer test discussed by Vukšić et al., the applicable ISO 20795-1 upper limit for Type 1, 3, 4 and 5 denture-base polymers is 2.2 mass% methyl methacrylate. Thick geometries also make uniform conversion and post-processing important, but conversion should not be inferred solely from residual-monomer content or vice versa. [5,13,34]

Vuksic et al. used HPLC to quantify residual monomer content in denture-base materials and reported values spanning approximately 0.05 to 3.2 mass% across manufacturing routes; the additively manufactured materials in that study were below the 2.2 mass% upper limit discussed by the authors. A later study reported water-solubility values of 3.01 and 3.22 µg/mm³ for two additively manufactured denture-base materials, above the 1.6 µg/mm³ limit applied in that test. Nitrogen post-curing has also been shown to improve conversion and cytocompatibility for a tested 3D-printed denture-base resin. [13,28,34]

The available evidence is comparatively strong for laboratory residual-monomer, water-sorption, water-solubility and mechanical testing. It is less developed for integrated long-term clinical studies linking these chemical endpoints to biological response over multi-year denture service. [13,34]

The principal uncertainties are therefore not a demonstrated general exceedance of the residual-monomer limit by additively manufactured denture bases, but the variability among materials, the relationship between laboratory chemical endpoints and long-term clinical response, and the effect of geometry and workflow on the cured network. [13,34]

7.3 Surgical guides and temporary contact devices

Surgical guides are typically used for short-duration contact in an invasive clinical context. Their qualification depends on intended purpose, contact type and the validated manufacturing and sterilisation process. Under the EU MDR, classification of a surgical guide depends on its intended purpose and the applicable classification rules; the device class should therefore be established for the specific guide rather than assigned generically. [2,19,30,45]

Sterilisation can affect dimensional, mechanical, surface or biological properties depending on method and material. Go et al. compared autoclave, ethylene-oxide and hydrogen-peroxide gas-plasma sterilisation for a printed implant surgical-guide resin and measured mechanical, physical and dimensional outcomes. Kronenberger et al. examined disinfection and sterilisation effects for printed resins used in cardiac-ablation guide applications. These studies support method-specific validation rather than a universal residual-species effect for every sterilisation technology. [21,30,45]

Rogers et al. reported ovo-toxic leachates from two Formlabs dental SLA resins and showed that oxygen-plasma surface treatment attenuated toxicity for one material but not the other. The study therefore provides material-specific evidence of ovo-toxicity and of a material-dependent response to oxygen-plasma surface treatment. The broader surgical-guide evidence remains stronger for short-term and process-specific endpoints than for comparative long-term biological response across sterilisation methods. [19,45]

Unresolved questions include how sterilisation method interacts with specific photopolymer chemistry, how repeated cycles affect a device qualified for reuse, and how dimensional and biological endpoints should be integrated for the intended surgical use. [21,30,45]

7.4 Biomedical scaffolds and tissue-contact research devices

Research-grade tissue-contact platforms use diverse photopolymer chemistries, cell models and biological endpoints. Studies include mesenchymal stromal-cell response to printed acrylates and organ-on-chip work in which wet-autoclave post-processing reduced leachable-related biological effects. [24,25,46]

Because research endpoints can include adhesion, proliferation, differentiation or organotypic function, the relevant biological question can be more granular than a single cytotoxicity screen. Extraction and cleaning methods therefore need to be interpreted in relation to the specific experimental system. [25,36,46]

The evidence base is heterogeneous and often consists of a small number of independent studies for any specific scaffold or organ-on-chip context. Standardised qualification approaches comparable to those used for established dental-device workflows remain incompletely developed in many exploratory research settings. [14,24,25,39,46]

7.5 Reusable or sterilised devices

Reusable printed devices introduce a temporal qualification problem because repeated cleaning or sterilisation can alter material properties. Available studies demonstrate material- and method-specific effects, but the evidence base is not yet sufficient to define a universal cumulative-cycle model for photopolymer devices. [21,30,45,46]

Autoclave, ethylene oxide, hydrogen-peroxide plasma and other sterilisation methods act through different physical or chemical mechanisms. Their effects should be described from measured endpoints for the specific material rather than inferred generically as a particular residual-species reaction in every photopolymer chemistry. [21,30,45,46]

Published studies document single-cycle or limited-cycle effects for several systems, while systematic comparisons across multiple cycle counts and multiple photopolymer chemistries remain rare. [21,30,45]

The principal unresolved question is how the validated cycle count and sterilisation method influence the finished device over its intended service life. This is particularly relevant where reuse is part of the intended purpose, but it should not be extrapolated to single-use devices. [21,30,45]

7.6 Application-specific evidence gaps

The five application contexts described in sections 7.1-7.5 share three recurring evidence gaps that constrain the conclusions available from the literature.

The first recurring gap is the correspondence between standardised characterisation protocols and clinical service-life biological response. Across the application space, the evidence base is more developed for endpoints accessible under short-term standardised protocols (cytotoxicity assays at 24-72 hours, residual monomer quantification at single time points, mechanical property characterisation at the point of fabrication) than for endpoints accessible only under longitudinal clinical observation (chronic exposure response, cumulative leaching, mechanical drift, microbial colonisation evolution). The relationship between the two endpoint classes is not consistently established. [14,17,31,32,34,35,44]

The second recurring gap is the integration of workflow variables into the evidence reporting. Studies of biological response across the application space typically document the formulation chemistry, the cell model, the extraction protocol and the biological endpoint, but document the workflow used to produce the cured specimens less systematically — print parameters, washing protocol, post-cure parameters and sterilisation conditions may be reported partially or referenced only by manufacturer brand. The influence of workflow variables on biological response cannot be fully reconstructed from the published literature, since the workflow variables are frequently absent from the published reports. [14,17,29,39,42]

The third recurring gap is harmonisation of additive-manufacturing-specific reporting and qualification methodology. ISO 10993 and ISO 20795-1 provide general or application-specific requirements, but the literature continues to show substantial heterogeneity in how printing, washing, post-curing, extraction and ageing conditions are reported. The gap is therefore best described as incomplete harmonisation rather than an absence of standards. [1,4,5,39,49]

Application class	Typical systems	Dominant biological concerns	Common post-processing considerations	Qualification constraints	Main evidence limitations
Direct-printed clear aligners [12,17,18, 31-33,35,40-44]	Proprietary urethane-(meth)acrylate, polyurethane and related photopolymer systems	Mucosal exposure; leachable monomers/additives; surface ageing; microbial interactions	Manufacturer-qualified cleaning and post-cure; atmosphere and centrifugation are system-specific	Device-specific ISO 10993 evaluation; ISO 10993-5 for cytotoxicity where applicable; ISO 10993-10 [47] for skin sensitization and ISO 10993-23 [48] for irritation as applicable	Long-term clinical biological data remain sparse; workflows and ageing protocols vary substantially
Denture base and prosthodontic devices [5,13,28,34]	Photopolymer denture-base systems with chemistry varying by manufacturer	Residual monomer or other extractables; water sorption/solubility; chronic mucosal exposure	Material-specific post-curing; surface finishing; atmosphere control where qualified	ISO 20795-1: residual MMA upper limit 2.2 mass% for the category discussed in [13]; water solubility upper limit 1.6 µg/mm ³ in [34]	Laboratory chemical endpoints are better characterised than multi-year integrated biological outcomes
Surgical guides and temporary invasive-contact devices [19,21,30,45]	Commercial dental/medical photopolymers qualified for defined workflows	Short-duration contact with surgically exposed tissue; process and sterilisation effects	Validated cleaning, post-cure and sterilisation method for the specific device	MDR classification is device- and intended-purpose-specific; biological evaluation according to applicable ISO 10993 endpoints	Few comparative studies integrate biological, dimensional and repeated-sterilisation outcomes
Research scaffolds and tissue-contact platforms [24,25,46]	Heterogeneous commercial and custom photopolymers	Cell viability, adhesion, proliferation, differentiation or organotypic function	Application-specific cleaning/extraction and surface treatment	Research qualification is endpoint-specific; clinical-device standards may inform but do not automatically define the experiment	Small, heterogeneous evidence base; limited cross-study comparability
Reusable or repeatedly sterilised devices [21,30,45,46]	Multiple chemistries depending on intended use	Cumulative changes in mechanical, surface and biological properties	Sterilisation method and cycle count validated for the device	Qualification must reflect intended reuse and validated cycle count where reuse is claimed	Systematic multi-cycle comparisons across chemistries remain rare

Table 1. Qualification landscape across application classes for additively manufactured photopolymer medical and dental devices.

8. Comparative synthesis

Five tensions recur across the formulation chemistries (section 5), workflow control practices (section 6) and application qualification contexts (section 7) examined in this review. The tensions are not particular to any single formulation approach, any single workflow practice or any single application; they appear in different combinations across the field and constrain the conclusions that can be drawn from the published evidence taken together. This section synthesises the five tensions and the recurrent patterns of evidence limitation associated with each. The intent is to map persistent incompatibilities documented in the evidence base rather than to propose their resolution.

8.1 Conversion versus extractables

The first recurring tension is between maximising conversion and minimising potentially releasable species. Conversion and residual-monomer or leachables measurements are related but non-equivalent. Berghaus et al. directly demonstrated conversion-leaching decorrelation, and aligner leaching studies show that chemistry and ageing influence release profiles. A robust characterisation therefore requires the appropriate combination of network-state and chemical-release measurements. [11,12,18]

8.2 Optical control versus bulk cure

Optical absorbers can improve control of cure depth during printing while also attenuating subsequent light penetration. The resulting balance is formulation-, wavelength- and geometry-dependent. Published work supports the existence of optical and processing interactions, but not a universal quantitative through-thickness conversion gradient for all pigmented systems. [29,38,40]

8.3 Manufacturability versus residual species reduction

Reducing low-molecular-weight reactive components can reduce one potential source of mobile species but can also change viscosity, cure kinetics and printability. The literature therefore supports treating formulation architecture as a trade-off space rather than assuming that monomer reduction alone determines biological response. [11,22,38]

8.4 Standardisation versus workflow heterogeneity

Cross-study comparison is constrained by differences in resin, printer, exposure, washing, post-curing, extraction and ageing protocols. ISO standards provide a common risk-management and testing framework, but published methodological choices remain heterogeneous, particularly for additive-manufacturing-specific workflows. [4,29,37,39]

8.5 Short-term qualification versus longitudinal uncertainty

Most biological-response studies use short-term in vitro endpoints, whereas clinical exposure can extend over weeks, months or years depending on the device. In vivo and artificial-ageing studies are beginning to address this mismatch, but they remain too heterogeneous to support a universal accelerated-ageing conversion or a single long-term exposure model. [16,31,32,35,44]

8.6 Persistence of the tensions across the evidence base

The five tensions described in sections 8.1-8.5 are not independent of one another. The conversion-extractables decoupling interacts with the optical control-bulk cure constraint through the formulation chemistry; the manufacturability-residual species tension interacts with the standardisation-workflow heterogeneity through the practical implementation choices made by device manufacturers; the short-term-longitudinal tension interacts with all the others through the temporal evolution of the cured network. The tensions therefore appear in combinations rather than in isolation, and the position of any specific commercial photopolymer system in the field is best described by the combination of tensions it accepts rather than by a single descriptor. [11,12,18,29,37,40]

A second observation across the synthesis is that the tensions are not artefacts of incomplete current knowledge that would be resolved by additional data. Each tension reflects a structural feature of photopolymer additive manufacturing as a manufacturing route — the chemistry of free-radical photopolymerisation, the optical physics of post-cure illumination through absorbing media, the rheology constraints of layer-wise processing, the workflow variability of multi-step post-processing, and the temporal evolution of cross-linked networks under service conditions. Additional data may quantify the magnitude of each tension more precisely for specific systems but is unlikely to eliminate the tensions themselves.

The principal consequence of this persistence is interpretive. Any claim about the biocompatibility of an additively manufactured photopolymer device that does not specify the position of the system within these five tensions is operating at a level of generality that the evidence base does not support. The system-level interpretation developed across sections 1-7 of this review emerges directly from this observation: biological response in photopolymer additive manufacturing is a function of the combination of formulation chemistry, workflow execution, application context and temporal exposure, and decoupling any of these in characterisation, in reporting or in regulatory documentation introduces interpretive ambiguity that the evidence base cannot resolve in retrospect. [1,4,39]

9. Recurrent absences in the evidence ecosystem

The synthesis in section 8 and the application-specific evidence gaps documented in section 7.6 converge on a set of recurrent absences in the published evidence ecosystem. Each absence has appeared repeatedly across the application contexts examined and across the formulation architectures surveyed, and each constrains the conclusions available from the literature in characteristic ways. The priorities listed below are formulated as observed gaps in the evidence base rather than as recommendations for what the field should do; the standardisation pressures associated with each are observed across the field as documented in the cited literature.

9.1 Standardised extractables methodology for additive manufacturing

Across the literature reviewed here, extractables and leachables studies use heterogeneous solvents, temperatures, durations, sample geometries and surface-to-volume ratios. ISO 10993-18 and ISO 10993-12 establish chemical-characterisation and sample-preparation principles, but additive-manufacturing-specific protocol choices remain incompletely harmonised across published studies. The resulting limitation is one of comparability, not an absence of an overarching standards framework. [4,11,12,18,37,49]

9.2 Longitudinal biological response under service conditions

Longitudinal biological-response data integrating chemical, mechanical and biological endpoints over the full service life of dental and biomedical photopolymer devices remain limited. Clinical-use and artificial-ageing studies provide partial evidence, but short-term cytotoxicity or single-time-point chemical measurements cannot yet be translated into a general long-term clinical response model. [1,16,17,31,32,35,44]

9.3 Workflow variable reporting in published biological response studies

Reporting of printer, exposure, washing, post-cure, storage and sterilisation parameters remains inconsistent across the literature. This limits reproducibility and makes it difficult to separate formulation effects from workflow effects when comparing studies. [14,17,29,39,42]

9.4 Quantitative characterisation of spatial conversion gradients

Across sections 3.2, 4.3, 5.5, 6.4 and 8.2, the published literature repeatedly acknowledges optical attenuation and workflow-dependent conversion, but quantitative through-thickness characterisation under defined formulation-geometry-workflow combinations remains underdeveloped. The evidence therefore supports describing spatial conversion as an incompletely characterised variable rather than claiming a complete absence of data or assigning a generic numerical gradient. [10,28,40]

9.5 Cumulative effects of sterilisation cycles on additively manufactured photopolymers

Published studies document effects of specific sterilisation methods on selected printed materials, including surgical-guide systems, but comparative work across multiple cycle counts and multiple photopolymer chemistries remains rare. The gap is therefore sparse cumulative evidence rather than an absence of sterilisation studies. [21,30,45]

9.6 Convergent character of the recurrent absences

The five recurrent absences documented in sections 9.1-9.5 are not independent of one another. The absence of standardised extractables methodology (9.1) limits the comparability of longitudinal biological response data (9.2) and constrains the reconstruction of workflow-dependent effects from the published literature (9.3). The absence of quantitative spatial conversion data (9.4) limits the interpretation of bulk extractables characterisation in pigmented geometries (9.1 again). The absence of cumulative sterilisation cycle data (9.5) interacts with the longitudinal biological response gap (9.2) for reusable devices specifically. Standardisation pressures observed in the field have begun to address some of these gaps individually; their convergent character suggests that the methodological harmonisation required is system-level rather than endpoint-specific. The recurrent absences are documented here as observations on the state of the evidence ecosystem; the resolution pathways available to the field are beyond the scope of this review. [4,14,17,29,37,39]

10. Limitations

The conclusions available from this review are constrained by three principal sets of limitations that derive from the state of the published evidence base, the temporal scope of the synthesis and the boundaries adopted for the analysis. Each limitation is documented here as a constraint on the inferences supported by the available data, not as a delimitation of authorial intent. The reader is invited to interpret the conclusions in section 11 within these constraints.

Limitation	Affected evidence	Consequence for interpretation	Typical methodological source
Incomplete workflow reporting [14,17,29,39,42]	Biological-response and application studies	Cross-study comparison and reproducibility are constrained	Printer, exposure, washing, post-cure, storage or sterilisation parameters incompletely reported
Non-harmonised extractables protocols [11,12,18,37,49]	Residual-species and leaching studies	Quantitative release values cannot be compared without accounting for extraction conditions	Different solvents, ratios, temperatures, durations, geometries and surface-to-volume ratios
Limited longitudinal evaluation [16,17,31,32,35,44]	Aligners and long-service dental devices	Short-term endpoints cannot be converted directly into long-term clinical biological response	Short in vitro assays, single-time-point chemistry, heterogeneous accelerated ageing
Sparse cumulative sterilisation-cycle evidence [21,30,45]	Reusable or sterilised devices	Cumulative effects across repeated cycles remain uncertain	Most studies evaluate one method or a limited number of cycles for a specific material
Underdeveloped spatial conversion characterisation [10,28,40]	Pigmented, opaque or thick geometries	Bulk chemical data are difficult to interpret without through-thickness network-state information	Optical attenuation is recognised, but quantitative formulation-geometry-workflow mapping is limited

Table 2. Recurrent limitations observed across the published evidence base on biocompatibility of additively manufactured photopolymer devices.

10.1 Constraints on cross-study comparison

The literature is methodologically heterogeneous. Studies apply different extraction protocols, cell models, exposure durations, biological endpoints and workflow reporting conventions. The present synthesis therefore emphasises qualitative patterns rather than quantitative pooling. Claims based on a specific material or test model have been retained only where the cited source supports that level of specificity. [14,17,19,24,25,37,43]

A second methodological constraint is the underreporting of workflow variables in published biological response studies (section 9.3). Many studies report the formulation chemistry, the cell model and the extraction protocol but document the workflow used to produce the cured specimens by reference to a manufacturer ecosystem rather than by parameter values. The workflow-dependent biological response patterns identified in this review cannot therefore be tested fully against the legacy literature, and conclusions about workflow-biology coupling are correspondingly preliminary. [14,17,29,39]

10.2 Constraints imposed by the temporal mismatch

Many qualification studies use short-term cytotoxicity, single-time-point chemical measurements or point-of-fabrication mechanical testing, whereas intended service can extend much longer. Intraoral and accelerated-ageing studies partly address this mismatch, but the relationship between laboratory ageing protocols and clinical time is not uniform across materials or endpoints. [1,13,16,31,32,34,35,44]

The temporal constraint operates in both directions for the analysis presented here. Studies of long-term clinical biological response that integrate mechanical, chemical and biological endpoints over multi-month-to-multi-year timescales are rare in the published literature, which limits the empirical support available for the temporal interaction dimension of the synthesis. The currently available evidence remains insufficient to determine the extent to which long-term temporal interactions modify biological response across different formulation-workflow combinations. The synthesis is therefore constructed within a partial temporal envelope, and conclusions about long-term biological response are correspondingly tentative. [16,31,32,35,44]

10.3 Constraints on the scope of the review

This review focuses on vat photopolymerisation in dental and biomedical contexts. It does not attempt to provide a complete review of material jetting, two-photon polymerisation or every microfluidic fabrication route. Regulatory standards and EU legislation are used as interpretive context rather than analysed exhaustively, and their status can change after the date of this revision. [1,2,4,5,6,7]

A further constraint is the evidence base itself. The review prioritises peer-reviewed journal articles, standards and primary regulatory sources available at the time of revision. Conference abstracts and unverifiable placeholder references present in an earlier working bibliography were not retained as evidence. The synthesis is therefore a dated evidence snapshot and should be updated if materially relevant new studies or regulatory changes appear.

11. Conclusions

The biocompatibility of additively manufactured photopolymer devices has been examined across formulation chemistry, workflow control practices, application qualification contexts, comparative tensions and recurrent absences in the evidence base. The synthesis supports four principal observations.

The first observation is that the published evidence is most consistent with the interpretation that biological response in photopolymer additive manufacturing emerges from the interaction between formulation chemistry, workflow variables, application context and temporal exposure, rather than from any single variable considered in isolation. This observation recurs across the formulation regions surveyed in section 5, across the workflow control practices documented in section 6, across the application qualification contexts examined in section 7, and across the comparative tensions synthesised in section 8.

The second observation is that the conversion-leaching decorrelation documented in the residual species literature (sections 4.1, 8.1) indicates that the chemical identity of the residual species — not simply their absolute quantity — appears to play a major role in leaching behaviour and biological response. This decorrelation has methodological consequences for the design of biocompatibility characterisation protocols, which the published evidence base has begun to address but has not yet resolved. [11,12,18,37]

The third observation is that the formulation design space for photopolymer additive manufacturing of medical and dental devices is multidimensional, and no formulation architecture simultaneously optimises conversion completeness, viscosity, optical control, mechanical flexibility, residual species reduction, hydrolytic stability, manufacturability and regulatory simplicity. Different applications occupy different positions in this multidimensional space, and the question for biocompatibility qualification is therefore not which formulation is superior, but which trade-off position matches the constraints of a given application and how the workflow translates that formulation choice into device-level biological outcome. [20,22,23,38,39]

The fourth observation is that the published evidence base on additively manufactured photopolymer biocompatibility is characterised by recurrent absences — standardised extractables methodology, longitudinal biological response data, systematic workflow variable reporting, quantitative spatial conversion gradients and cumulative sterilisation cycle effects — that interact across endpoints and applications rather than remaining isolated to single methodological dimensions. These absences constrain the conclusions available from the literature taken together and shape the standardisation pressures observed across the field. [4,14,17,21,29,37,39,45]

The available evidence does not support universal claims about the biocompatibility of any specific formulation chemistry, workflow architecture or application context considered in isolation. The available evidence does support the interpretation that the formulation, the workflow, the application and the temporal context constitute a coupled qualification environment in which characterisation, reporting and regulatory documentation are difficult to interpret independently from one another within the published evidence base. The development of the evidence base through standardisation initiatives, longitudinal studies and more systematic workflow reporting in published biological response studies is observed across the field; the resolution pathways available to each of these directions are subjects for the empirical and regulatory work that follows. [1,2,4,39]

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J. Segurola is founder and Scientific Director of Resyner Technologies S.L. / 3Dresyns, a company active in the development of photopolymer materials for additive manufacturing. The review is based on the cited published literature; commercial products, including products from 3Dresyns where represented in that literature, are discussed only in relation to the cited evidence.

CRedit authorship contribution statement

Juan Segurola: Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review and editing.

Data availability

No data were generated for this research. All sources analysed are cited in the reference list.

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