

ER-92

Residual Reactants, Impurities and Manufacturing Conversion as Hidden Drivers of Photopolymer Hazard

Free (Meth)acrylic Acids, Hydroxyalkyl Monomers, Technical-Grade Composition and Residual Extractables in UV/VPP Systems

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Keywords: acrylate; methacrylate; impurity; residual monomer; acrylic acid; methacrylic acid; HEA; HEMA; extractables; VPP.

Statement of Significance

A photopolymer hazard record can be misattributed when the nominal ingredient name is treated as if it described a chemically pure material. Commercial reactive monomers can contain structurally related monoesters, hydroxyacrylates, free acid, inhibitor and other process-derived constituents; oligomer synthesis can leave residual low-molecular-weight reactants; and the printed network can retain extractable unreacted species after exposure. ER-92 examines when those residuals are biologically material and how to separate them analytically. The review finds strong evidence that impurities can change sensitisation attribution, but it does not support the universal claim that residual acrylic or methacrylic acid is the dominant cause of irritation in acrylate systems. That proposition remains formulation- and batch-specific and must be measured rather than assumed.

Abstract

Technical-grade (meth)acrylates are often treated in formulation discussions as single molecular species. Historical analytical work shows why that simplification can fail: commercial patch-test diacrylates were reported at 81–91% purity, with tripropylene glycol diacrylate containing 13% tripropylene glycol monoacrylate, while triacrylates were 82–86% pure and the corresponding hydroxyacrylates occurred at 1–13% [1]. Clinical evidence demonstrates that an impurity can become the causal sensitizer: acrylic acid present as an impurity in an ECG electrode hydrogel was identified by HPLC and positive patch testing as the cause of allergic contact dermatitis [4]. Conversely, a systematic irritation study of residual (meth)acrylic monomers found HEA to be the most potent dermal irritant among the tested compounds, cautioning against a general assumption that free acrylic or methacrylic acid necessarily dominates irritation [6]. For VPP, the problem continues after formulation: incomplete conversion and post-processing leave extractable residual monomers, and washing and post-processing conditions can materially change their elution and biological response [9,10]. ER-92 therefore proposes a three-state qualification architecture: raw-material composition, uncured-resin/oligomer residuals, and cured-part extractables. Hazard attribution should follow compound-specific analytical evidence rather than nominal ingredient identity, acid number alone or SDS wording.

1. Scope and boundaries

ER-92 owns the compositional question that sits between synthetic chemistry and biological testing: what unreacted or unintended low-molecular-weight species are actually present in the raw monomer, oligomer, uncured resin and cured article, and can they change hazard attribution? ER-91 owns evidence-density and SDS asymmetry. ER-93 owns occupational dermatitis epidemiology and prevention. ER-94 owns intrinsic molecular structure-hazard relationships. ER-80 owns in-can stability, including the effect of residual hydroxyalkyl monomers and free acids on storage chemistry. ER-86 owns extractables-and-leachables qualification as a broad finished-device discipline. ER-95 owns

photoinitiator migration, substitution and photolysis-product extractables. ER-92 is narrower: it asks whether composition that is hidden by the nominal chemical name can be the source of the observed hazard.

2. Nominal identity is not analytical composition

Polyfunctional acrylates are particularly vulnerable to shorthand descriptions because commercial materials can be distributions rather than ideal single structures. Henriks-Eckerman and Kanerva analysed (meth)acrylate patch-test substances by GC/MS [1]. Their dimethacrylates were 97–99% pure, but three diacrylates were only 81–91% pure and the triacrylates 82–86%. TPGDA at 81% purity contained 13% tripropylene glycol monoacrylate, and all examined diacrylates and triacrylates contained 1–13% of corresponding hydroxyacrylates. The authors explicitly warned that such impurities can cause false interpretation of patch-test results and recommended batch-specific purity reporting.

This result is directly relevant to historical comparisons among HDDA, TPGDA, TMPTA and related reactive diluents. A clinical reaction assigned to a trade or generic monomer name may reflect the major constituent, a minor related acrylate, cross-reaction, concomitant sensitisation, or a combination. Kanerva, Jolanki and Estlander later warned that patch-test frequencies cannot be read as a ranking of sensitising capacity without exposure histories and compound-purity information, because acrylate-containing products regularly contain undeclared acrylates [2].

3. Free acid is a separate compositional variable

Hydroxyethyl acrylate and hydroxyethyl methacrylate illustrate why “the monomer” and “the batch” are different levels of description. The OECD SIDS Initial Assessment Report for hydroxyethyl acrylate describes a typical commercial HEA sample as greater than 96.5% HEA with, among other constituents, acrylic acid at up to 1% w/w [7]. A high-purity HEMA specification from GEO separately limits acidity, expressed as methacrylic acid, to 0.05% w/w while also specifying diester impurities [M1]. These examples do not establish universal concentrations across suppliers. They demonstrate that free AA/MA is a recognised analytical specification variable and can differ materially with grade and purification.

Acid number is useful as a bulk process-control variable but is not compound-specific. A measured acid value cannot by itself distinguish acrylic acid, methacrylic acid, acidic oligomer end groups, hydrolysis products or other acidic constituents. When hazard attribution depends on free AA/MA, compound-specific chromatography or another validated selective method is required. This is especially important for urethane (meth)acrylate oligomers: residual HEA/HEMA and free acid should be treated as independently measurable quantities rather than inferred from the oligomer name or from a single acid-number result.

4. Impurities can be the causal allergen

The strongest direct clinical example is the ECG-electrode study of Stingeni et al. [4]. The patient reacted to the electrode hydrogel even though separate nominal constituents did not reproduce the reaction. HPLC then showed acrylic acid as an impurity; subsequent patch testing to acrylic acid was positive, and the authors attributed the sensitisation to the impurity. Positive reactions to HEMA, HPMA and EGDMA were interpreted as cross-reactions. This is exactly the kind of case that nominal-ingredient reasoning can miss.

The reverse can also occur at the raw-material level. Waegemaekers and van der Walle found a strongly sensitising constituent in commercial acrylic acid and identified alpha,beta-diacryloxypropionic acid (DAPA), a synthesis-related secondary product, as the responsible impurity; distilled acrylic acid did not contain the sensitising impurity [5]. Thus even “free acrylic acid” is not automatically a chemically uniform hazard source. Purity can change the biological attribution in both directions.

5. Irritation and sensitisation must not be conflated

The hypothesis that residual AA/MA may intensify an irritation result is chemically plausible and should be tested where free acid is high, but ER-92 does not elevate it to a universal mechanism. Tokumura et al. compared seven acrylic and three methacrylic monomers by cytotoxicity (MTT, EC50) in a cultured dermis model, used to set dose levels for a subsequent rabbit primary-irritation test [6]. HEA showed the strongest dermal irritation in that panel, with the lowest erythema dose, while the other tested monomers, including AA, MAA and HEMA, were less potent under those test conditions. This directly contradicts any blanket statement that free acid must be the principal irritant whenever it is present.

Sensitisation is a different endpoint again. Sasseville's review notes that multiple positive acrylate patch tests may reflect cross-reactions, concomitant reactions and impurities not disclosed in SDS [3]. A formulation can therefore produce an irritation signal, a sensitisation signal, or both, and the responsible species need not be the same. Batch-specific analytical chemistry must be linked to the specific biological endpoint.

Table 1. Composition variables that can confound hazard attribution

Variable	Example evidence	Potential attribution error	Preferred control
Related mono-/di-/triacrylates	TPGDA sample containing 13% monoacrylate; hydroxyacrylates 1–13% [1]	Reaction assigned to the nominal major monomer	GC/MS or LC/MS purity profile by batch
Free AA / MAA	HEA data include AA as a possible commercial constituent [7]; HEMA HP separately specifies MAA acidity [M1]	Acid contribution ignored or assumed without measurement	Compound-specific free-acid assay plus acid number
Hidden sensitising impurity	AA impurity causal in ECG electrode [4]; DAPA impurity in commercial AA [5]	Wrong molecule receives causal attribution	Targeted chromatography linked to patch-test result
Residual monomer after cure	HEMA/TEGDMA elution changed by washing [9]	Raw-resin SDS treated as complete finished-part evidence	Extractables analysis on defined cured/post-processed state
Conversion / network state	DLP resin residuals affected cell adhesion [10]	Biological response attributed only to ingredient list	Degree of conversion plus extract/cytotoxicity testing

6. Residual HEA/HEMA in oligomers: measure, do not infer

Hydroxyethyl acrylate and HEMA are widely used as reactive hydroxy-functional building blocks and can also appear as impurities or residual monomers. In an oligomer synthesis, the amount remaining after reaction depends on stoichiometry, conversion, purification, hydrolysis history and any deliberate use of reactive diluent. ER-92 therefore treats “residual HEA/HEMA in a urethane acrylate” as an analytical question, not as an unavoidable property of the oligomer family. A supplier certificate or internal QC method that directly measures free HEA/HEMA is much stronger evidence than the name “urethane acrylate”, an acid number, or a presumed synthesis route.

This distinction also prevents a circular toxicological argument. If a technical oligomer produces a strong irritation or sensitisation result, one cannot conclude that the oligomer backbone is intrinsically responsible until residual low-molecular-weight constituents have been characterised. Conversely, finding residual HEA/HEMA does not prove causality without exposure-relevant concentration and biological evidence.

7. The VPP process creates a second residual-monomer problem

Even a well-characterised raw resin becomes a different chemical state after photopolymerisation. Conversion is incomplete, an oxygen-inhibited surface may remain, and unreacted or weakly bound species can be removed by washing or later extracted from the network. Jin et al. quantified this directly in DLP-printed crown-and-bridge resin: ultrasonic washing reduced residual HEMA from 2.0634 ppm to 0.1456 ppm and TEGDMA from 1.4862 ppm to 0.1484 ppm across the studied washing conditions, while cytotoxicity decreased as washing time increased [9]. The study also demonstrated a trade-off because excessive washing altered mechanical properties.

Alt, Heinemann and Kruppke examined four DLP acrylate resins and found that released resin residuals influenced cell adhesion in an indirect cytotoxicity assay [10]. The important engineering point is not that every printed acrylate is cytotoxic. It is that “raw formulation composition”, “degree of conversion” and “extractable residual composition” are separate evidence states. Finished-part biological qualification cannot be inferred from raw-material hazard labels alone.

8. Three-state analytical architecture for VPP

Table 2. Minimum composition record across the VPP material-state chain

State	Minimum questions	High-value measurements	Decision use
A. Incoming raw material	What is the actual batch composition and purity?	Assay; free AA/MA; related acrylates; inhibitor; water; identified	Prevents nominal-name substitution for composition

State	Minimum questions	High-value measurements	Decision use
		process impurities	
B. Oligomer / uncured resin	What residual reactants remain after synthesis and formulation?	GC/LC profile; acid number plus selective acid assay; free HEA/HEMA; stability trend	Separates synthesis conversion from formulation hazard
C. Printed / post-cured article	What species are extractable after the declared process?	Degree of conversion; surface wash validation; targeted + non-targeted extractables; cytotoxicity where relevant	Connects process state to actual user/device exposure

9. Implications for SDS and hazard communication

An SDS normally communicates the classified substance or mixture within regulatory disclosure rules; it is not a complete chromatogram and is not intended to list every trace constituent. This creates two practical consequences. First, an impurity below a disclosure threshold can still matter to a previously sensitised individual. Second, absence of a constituent from an SDS cannot substitute for analytical proof that it is absent. Aalto-Korte and Suuronen found that occupational acrylic-allergy investigations often required chemical analysis when SDS did not reveal the compounds implicated by patch testing [8].

For internal material selection, the appropriate response is not to “correct” the SDS but to add an analytical layer. The COA, supplier specification and independent or internal assay should be treated as composition evidence; the SDS remains hazard-communication evidence. When the two tell different stories, the discrepancy is itself a qualification issue.

10. Qualification workflow

- Define the nominal component and obtain the current SDS, TDS and certificate of analysis for the exact batch or representative manufacturing grade.
- Measure purity with a method capable of resolving structurally related mono-, di- and tri-functional acrylates; do not rely on one bulk assay when the biological hypothesis is compound-specific.
- Measure free acrylic and methacrylic acid selectively when they are part of the hazard hypothesis; retain acid number as a complementary, non-specific process variable.
- For oligomers, quantify residual low-molecular-weight HEA/HEMA or other reactants when their presence is chemically plausible. Do not infer the concentration from synthesis stoichiometry alone.
- After VPP, define washing and post-cure state before measuring residuals or extractables. A cured part without its process history is not a reproducible test article.
- Link analytical findings to the biological endpoint. Irritation, sensitisation, cytotoxicity and systemic endpoints require separate causal reasoning.

11. Limitations and research gaps

The literature contains compelling examples of impurity-driven hazard attribution, but it does not establish that free AA/MA or residual HEA/HEMA explains most historical irritation from UV-curable formulations. The strongest directly retrieved irritation comparison [6] actually places HEA above AA/MA under its test conditions. Likewise, public HEA and HEMA specifications demonstrate that free acid is controlled as an impurity variable, but supplier specifications are not prevalence surveys across the industry.

A decisive future study would take multiple production batches of the same nominal monomer or oligomer, quantify free acid and related reactive impurities, perform validated irritation/sensitisation testing on compositionally characterised material, and then re-test after selective purification or spiking. That design would determine whether a biological endpoint tracks the nominal monomer or a specific residual constituent.

12. Conclusions

The practical conclusion is stronger than either “the monomer SDS tells the whole story” or “the impurity is always to blame”. Both are inadequate. Technical-grade acrylates can contain substantial related reactive species; clinical cases prove that an impurity can be the causal allergen; and VPP introduces a second residual pool through incomplete conversion and post-processing. At the same time, available irritation data do not support a universal rule that acrylic or methacrylic acid dominates the skin response.

A defensible hazard assessment therefore follows the material state. Characterise the incoming monomer or oligomer, quantify relevant residual reactants in the formulated resin, and measure extractables from the defined printed/post-cured article. Only after those layers are separated should a biological effect be attributed to the nominal monomer, to a residual acid, to HEA/HEMA, to another impurity, or to the cured network.

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Version note

v0.2 is a release incorporating independent review corrections

review. The v0.1 attribution and method-description issues were corrected or rechecked against accessible authoritative records; The declared verification gates were completed.