

ER-94

Monomer Structure-Hazard Relationships in Photo-Curable (Meth)acrylates: Electrophilicity, Functionality, Molecular Architecture, Cross-Reactivity and Limits of Read-Across

Why molecular structure can prioritise hazard testing but cannot replace compound-specific evidence

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Statement of Significance

Formulators routinely use molecular structure to anticipate reactivity, viscosity and network formation, but hazard cannot be collapsed into the same shorthand. Acrylate versus methacrylate substitution, reactive-functionality count, molecular size, backbone polarity and impurity profile can influence electrophilic reactivity, skin sensitisation and exposure, yet the direction and magnitude depend on the endpoint and the chemical series being compared. ER-94 establishes a disciplined structure-hazard framework: use molecular architecture to define mechanistic hypotheses and testing priorities, never as a universal ranking that substitutes for compound-specific toxicology, composition or exposure evidence.

Abstract

Photo-curable (meth)acrylates share structural motifs that invite structure-activity reasoning, particularly the alpha,beta-unsaturated carbonyl system of acrylates and the alpha-methyl substitution of methacrylates. Experimental studies show that electrophilic reactivity toward glutathione can vary by orders of magnitude and that alpha-methyl substitution reduced thiol reactivity for selected acrylate/methacrylate pairs. Guinea-pig sensitisation studies likewise demonstrate meaningful differences between multifunctional acrylates, but they do not support a simple monotonic rule based on functionality count alone. Closely related bisphenol-A/epoxy-derived di(meth)acrylates showed sharply different sensitising capacities, with impurities identified as a potentially important confounder. Contemporary reviews of methacrylate skin-sensitisation methods show that in vitro, in chemico, animal and in silico approaches do not perform identically across even a deliberately bounded chemical series. Clinical literature further shows asymmetric cross- and co-sensitisation patterns. ER-94 therefore separates five questions: molecular electrophilicity, intrinsic sensitisation endpoint, exposure/mobility, technical-grade composition, and clinical cross-reactivity. Structure can support hypothesis-driven read-across only when the endpoint, applicability domain, impurities and contradictory data are addressed. It cannot establish that one untested monomer is "safer" than another.

1. Scope and controlling boundaries

ER-94 asks what can and cannot be inferred about hazard from monomer structure in photo-curable (meth)acrylate chemistry. It covers mechanistic descriptors, sensitisation evidence, cross-reactivity and read-across discipline. It does not rank commercial monomers or disclose a 3Dresyns formulation-selection rule.

ER-91 controls evidence-density and SDS-expression asymmetry; ER-94 does not explain a sparse record by assuming lower hazard. ER-92 controls impurities, residual reactants and manufacturing conversion; ER-94 treats purity as a confounder and hands composition attribution back to ER-92. ER-93 controls occupational dermatitis diagnosis, exposure and prevention; ER-94 discusses sensitisation and cross-reactivity only as hazard endpoints. ER-95 controls photoinitiator substitution. ER-27 controls conversion measurement. No internal relationship between functionality, molecular weight and VPP bleeding, cure growth or XYZ resolution is part of ER-94.

2. A structure-hazard statement must name the endpoint

A chemical structure can influence several different properties: electrophilic reaction rate, volatility, skin permeation, protein binding, cytotoxicity, irritation, sensitisation, genotoxicity and environmental toxicity. These are not interchangeable. A mechanistic descriptor that predicts one endpoint in a defined series does not automatically predict another endpoint or a finished-resin outcome.

Structural descriptor	Mechanistic relevance that may be tested	What it does not establish
Alpha,beta-unsaturated acrylate carbonyl	Potential Michael-acceptor electrophilicity toward nucleophiles.	Clinical sensitisation potency, systemic toxicity or safe-use concentration by itself.
Alpha-methyl substitution (methacrylate)	Can reduce electrophilic thiol reactivity in selected paired series [2].	Universal absence of sensitisation or irritation.
Number of reactive (meth)acrylate groups	Changes molecular functionality and may alter opportunities for reaction and network formation.	Monotonic hazard ranking across different backbones, purities and endpoints.
Molecular size / polarity	Can influence mobility, exposure and biological accessibility.	Intrinsic sensitisation potency without endpoint-specific data.
Aromatic / ether / urethane / hydroxyl architecture	Changes electronic, steric and physicochemical context.	A transferable class label such as "safe urethane acrylate" or "hazardous aromatic".
Technical-grade impurity profile	May introduce a different causal species from the nominal monomer [7].	Intrinsic property of the idealised pure structure.

3. Electrophilicity: useful mechanistic evidence, bounded endpoint

Autian provided an early structure-toxicity treatment of acrylic monomers across multiple industrial contexts [1]. That historical framework is useful for showing why molecular architecture matters, but modern hazard interpretation requires narrower endpoints and better-defined chemical series.

McCarthy et al. directly compared selected acrylate and methacrylate esters against glutathione and found that acrylate electrophilic reactivity decreased with alpha-methyl substitution in the paired systems studied [2]. The same work did not justify equating thiol reactivity with every toxicological endpoint. Schultz et al. later verified structural alerts for Michael acceptors using glutathione as a model nucleophile across a broader set of electrophiles [3]. Böhme et al. quantified glutathione reaction rates for multiple electrophile classes and reported rate constants spanning approximately five orders of magnitude [4].

The engineering conclusion is deliberately narrow: electrophilic reactivity is a mechanistically informative descriptor for Michael-acceptor chemistry and can help define an applicability domain. It is not a universal hazard score. A compound can be less reactive in one nucleophile assay and still require independent evidence for irritation, sensitisation, genotoxicity or application-specific exposure.

4. Acrylate versus methacrylate is a trend, not a verdict

The alpha-methyl group in methacrylates changes the electronic and steric environment of the double bond. In the McCarthy series, this reduced electrophilic reaction with glutathione for paired acrylate/methacrylate esters [2]. However, occupational and clinical data clearly demonstrate that methacrylates can still be important sensitisers. De Groot and Rustemeyer identify HEMA as a frequent patch-test-positive methacrylate and discuss substantial cross- and co-sensitisation [10]. Therefore, "methacrylate" cannot be converted into "non-sensitising" or "safe".

5. Functionality count does not create a universal hazard ladder

Björkner tested multiple multifunctional acrylates in the guinea-pig maximisation test and observed differing sensitising capacities: BUDA and HDDA were moderate-to-strong sensitisers, TPGDA was moderate, and other structures produced different outcomes [5]. In separate work, TMPTA was a strong allergen in the guinea-pig maximisation test and was associated with dermatitis in printing workers [6].

These data establish that multifunctional acrylates can be potent sensitisers, but they do not justify a scalar rule such as "more functional groups = more hazardous". Functionality is entangled with spacer length, molecular geometry, electronic effects, purity, exposure and the test endpoint. ER-94 therefore permits functionality as a screening descriptor but prohibits it as a stand-alone hazard rank.

6. Closely related backbones can diverge sharply

Björkner, Niklasson and Persson compared di(meth)acrylates based on bisphenol A or epoxy-resin structures in the guinea pig [7]. Some closely related compounds were strong sensitisers while others had low or no sensitising capacity in that study. Crucially, the authors attributed the sensitising activity of one chromatographic fraction not to the nominal monomer but to a residual epoxy species of molecular mass 340 present in it [7]. This is the cleanest boundary with ER-92: an apparent structure-hazard relationship can be distorted when the tested material is a technical mixture rather than the idealised named molecule.

7. Cross-reactivity is not the same as structural similarity

Clinical co-positivity can reflect cross-sensitisation, co-exposure, shared impurities or independent sensitisation. Aalto-Korte et al. analysed concomitant reactions in 66 patients with occupational acrylic-monomer allergy and reported asymmetric patterns: exposure to methacrylates may induce cross-reactivity to acrylates, whereas exposure to acrylates usually did not lead to cross-allergy to methacrylates in their dataset [11]. De Groot and Rustemeyer likewise review strong cross-allergy among HEMA, EGDMA and hydroxypropyl methacrylate while cautioning that multiple positive reactions require clinical interpretation [10].

ER-94 therefore does not infer cross-reactivity from a substructure match alone. Structural similarity can motivate a testing hypothesis; the clinical conclusion belongs to exposure history and diagnostic evidence under ER-93.

8. Test method and applicability domain matter

Kimber reviewed a bounded methacrylate series across animal, in vitro and in silico sensitisation methods [8]. The scope restriction is important: a model evaluated within one bounded methacrylate series should not be silently transferred to monomers containing additional rings, heteroatoms or reactive functions. In the follow-up analysis, DPRA and ARE-Nrf2 luciferase methods performed well in comparison with animal-test results and available human sensitisation data, whereas EpiSensa and h-CLAT were more problematic and the DEREK-nexus and TIMES-SS QSAR approaches did not reflect sensitisation potential accurately for that series [9].

The correct use of a QSAR or non-animal method is therefore endpoint- and domain-specific. A prediction should report the model, applicability domain, structural analogues, uncertainty and contradictory experimental evidence rather than only the predicted label.

9. Purity and composition are part of the structure-hazard problem

A nominal monomer name can hide inhibitors, monoesters, hydroxy-functional by-products, free acid, oligomeric species and other technical-grade constituents. ER-92 owns that analytical composition question. ER-94 uses one rule only: when a hazard observation could plausibly be driven by an impurity or mixture component, do not attribute it to the idealised main structure without analytical evidence. The 1984 bisphenol/epoxy di(meth)acrylate study provides direct precedent for this caution [7].

10. Read-across must be hypothesis-driven

ECHA describes grouping and read-across as a data-gap approach that requires justification under REACH and explicitly recommends a hypothesis-driven explanation for why source-substance data can predict the target property [R1]. Its Read-Across Assessment Framework emphasises structured assessment of similarities, differences, supporting evidence and shortcomings. Structural similarity is therefore necessary context in many read-across cases, but not sufficient evidence by itself.

Read-across gate	Required question	Failure mode
Endpoint match	Is the source evidence for the same hazard endpoint being predicted?	Use cytotoxicity or electrophilicity as a surrogate for sensitisation without justification.

Read-across gate	Required question	Failure mode
Chemical identity	Are source and target structures, stereochemistry, salts/mixtures and relevant impurities defined?	Compare trade names or nominal families only.
Mechanistic hypothesis	Why should the structural difference preserve or alter the endpoint?	"Both are acrylates" used as the entire rationale.
Applicability domain	Does the model/source series contain the target structural features?	Extrapolate from simple esters to complex multifunctional monomers without evidence.
Contradictions	Do any experimental data oppose the proposed trend?	Discard inconvenient results as outliers without analysis.
Uncertainty	What remains unmeasured and how does that affect the decision?	Convert a screening prediction into a finished safety claim.

11. Engineering screening matrix

	Permitted use of structure	Evidence still required
1. Hypothesis	Identify electrophilic motifs, alpha substitution, functionality, polar groups and plausible analogues.	Exact substance identity and technical-grade composition.
2. Prioritisation	Flag structures for focused sensitisation, irritation or reactivity testing.	Endpoint-specific test method in a valid domain.
3. Comparison	Use matched analogues to interpret directional trends.	Contradiction search, impurity control, uncertainty.
4. Read-across	Build a documented hypothesis and data matrix under an accepted framework.	Regulatory/scientific justification for the specific endpoint.
5. Formulation decision	Use hazard evidence as one input to selection.	Exposure, residuals/conversion, performance and intended-use qualification in neighbouring ERs.

12. Prohibited shortcuts

- Do not state that all methacrylates are safer than corresponding acrylates.
- Do not convert functional-group count into a universal sensitisation or toxicity rank.
- Do not infer clinical cross-allergy from molecular similarity alone.
- Do not attribute a technical-grade hazard result to the main named monomer when impurities are uncontrolled.
- Do not use one in chemico reactivity assay as a substitute for endpoint-specific hazard data.
- Do not transfer a QSAR result outside its declared applicability domain without explicit justification.
- Do not publish proprietary 3Dresyns relationships between molecular architecture and print-resolution, bleeding or cure-growth behaviour.

13. Research and standardisation priorities

The most useful next step is not a larger list of structural alerts, but better matched chemical series in which purity, substitution pattern, functionality, molecular size and the hazard endpoint are controlled independently. Comparative datasets should include exact substance identity, measured composition, a mechanistically relevant reactivity descriptor, at least one endpoint-specific hazard method and transparent uncertainty. Such datasets would allow structure-based screening to become more quantitative without disguising the limits of the applicability domain.

- Matched acrylate/methacrylate pairs with controlled purity and the same backbone.
- Multifunctional series that vary one structural feature at a time rather than several simultaneously.
- Explicit testing of whether technical-grade impurities explain apparent outliers in sensitisation datasets.
- Cross-method datasets linking in chemico reactivity, non-animal sensitisation methods and historical reference evidence within the same chemical set.
- Read-across reports that publish the analogue matrix, contradictions and uncertainty rather than only the final predicted category.

14. Conclusions

Molecular structure is indispensable for asking better hazard questions, but insufficient for answering them by itself. The strongest reproducible trend in the present evidence is mechanistic: alpha-methyl substitution can reduce electrophilic thiol reactivity in selected acrylate/methacrylate pairs, while Michael-acceptor reactivity spans a wide range across structures. Sensitisation evidence is more conditional. Multifunctional acrylates can be strong sensitisers, yet functionality count is not a monotonic hazard scale; closely related bisphenol/epoxy-derived monomers can diverge sharply; and technical-grade impurities can change attribution. Clinical cross-reactivity introduces another layer that cannot be solved by substructure matching alone. The defensible rule is therefore: structure -> hypothesis -> endpoint-specific evidence -> composition/exposure check -> bounded read-across, never structure -> hazard verdict.

Limitations

This review focuses on structure-hazard reasoning for (meth)acrylate monomers and skin-sensitisation/electrophilicity evidence because those endpoints have the clearest comparative literature. It does not claim that the same structural trends predict every systemic, genotoxic, reproductive or environmental endpoint. Historical animal data are used as evidence records, not as a recommendation for new animal testing.

Author contributions

Juan Seguro: conceptualisation, literature synthesis, engineering framework, writing and critical review.

Competing interests

The author is founder, CEO and CTO of 3Dresyns by Resyner Technologies S.L. No proprietary formulation, supplier, concentration, screening window or internal structure-printability heuristic is disclosed.

Data availability

No new experimental dataset was generated. Statements derive from the cited peer-reviewed literature and public regulatory guidance.

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Regulatory read-across guidance

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