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Safety Assessment for Fluorinated Compounds: Use of PFAS Analogue Data in Recent Read-Across Decisions

When substance-specific data are limited, analogue comparisons can play an important role in safety assessment. For manufacturers of fluorinated compounds, this creates a challenge: a substance that is not itself a PFAS may still be assessed using data from a PFAS or another fluorinated substance that regulators consider sufficiently similar.

Structural similarity may provide a starting point for selecting an analogue, but it does not necessarily establish similarity in biological response, potency, or toxicokinetics. Transcriptomic and toxicokinetic evidence can help test the underlying read-across hypothesis by asking whether the substances behave similarly in biological systems and at exposures relevant to the safety decision.

In this article, we look at recent EPA examples of analogue-based assessment and what ScitoVation's published research demonstrates about testing structural similarity with biological and toxicokinetic evidence.

What recent EPA notices show about analogue-based assessment

EPA notices published this year show how analogue data have influenced the assessment of fluorinated compounds. Photolithography chemicals provide an example of EPA using PFAS analogue data as part of an assessment. In its July 23, 2026 proposed significant new use rule, EPA described Premanufacture Notices (PMNs) P-25-98 and P-25-99 as sulfonium salts intended for photolithography, each consisting of a sulfonium cation paired with a polyfluoropolyhydro anion¹. EPA applied different comparison bases to different parts of the same molecule. For the cations, it cited comparison to chemical substance analogues to flag acute toxicity, skin and respiratory irritation, and neurological effects. For the anions, EPA cited comparisons with PFAS analogues that raised concerns about systemic, reproductive, and developmental toxicity. EPA also considered submitted genotoxicity data for P-25-99; therefore, analogue information was one part of the overall evidence base rather than the sole basis for the assessment¹.

Display materials provide additional examples of analogue-based assessment². In a June 5, 2026 proposal, EPA described P-24-152, a phenyl carboxylic acid ester, alongside P-24-153, a fluoro-substituted polyphenyl alkyl, and P-24-154, a polyphenyl ethoxy-polyfluoro-alkyl, all intended for use as display materials². Based on comparison to chemical substance analogues, EPA identified systemic effects concerns for all three substances and reproductive effects concerns for P-24-153 alone. A separate aquatic toxicity prediction for P-24-154 combined submitted test data with comparison to neutral organic analogues. In contrast to the photolithography example, EPA did not identify these comparator substances as PFAS,

although it separately characterized P-24-153 and P-24-154 as potentially persistent, bioaccumulative, and toxic².

In both cases, the underlying Toxic Substances Control Act (TSCA) orders predate the published notices, January 2026 for the photolithography pair and July 2025 for the display materials. This timing clarifies when the underlying regulatory concerns first emerged^{1,2}. These examples demonstrate how analogue selection can contribute to hazard identification and subsequent regulatory decisions for fluorinated compounds, with the basis for comparison differing by substance and endpoint.

What does this mean for read-across arguments?

The EPA examples raise an important question for manufacturers whose fluorinated compounds are assessed using data from proposed analogues: does the similarity used to select an analogue translate into biological similarity relevant to the hazard being assessed?

Structural similarity can provide a useful starting hypothesis for analogue assessment, but it does not establish that two substances reach the same tissues, engage the same mechanisms, or produce comparable effects at relevant exposures. On the other hand, a different overall gene-expression pattern does not automatically rule out a shared mechanism for a particular adverse effect.

A read-across argument therefore needs to test the similarities that matter for the endpoint and decision. Table 1 summarizes some of the key questions to consider.

Table 1. Evidence and questions for evaluating a read-across argument.

Evidence	Question for the read-across argument
Structure and transformation	Are the parent chemicals, ions, metabolites, and degradation products appropriately compared?
Transcriptomic response	Are the relevant pathways and concentration-response patterns concordant in a suitable biological system?
Toxicokinetics and exposure	Do absorption, clearance, and internal concentrations support the proposed extrapolation?

ScitoVation research: Testing biological similarity

ScitoVation's published work provides examples of how the biological basis for a proposed read-across can be tested. Although the study by Barutcu et al., published in 2026, involved nitroparaffins rather than fluorinated compounds, it demonstrates how transcriptomic and toxicokinetic evidence can be used to determine whether structural similarity is accompanied by similarities in biological response and internal exposure.

- **Nitroparaffins: Testing a proposed read-across.** Work published by Barutcu et al. and Advancion compared nitromethane, nitroethane, and 1-nitropropane to assess the biological basis for extending nitromethane carcinogenicity information to the other two

nitroparaffins³. In primary rat hepatocytes, the compounds showed limited overlap in altered genes and enriched pathways. In vitro to in vivo extrapolation also indicated differences in systemic bioavailability and clearance. These findings did not support an assumption of equivalent biological behavior based on structure alone and instead supported a chemical-specific assessment. This challenged that particular read-across argument, but it did not show that the other compounds were free of carcinogenic hazard³.

- **PFAS: Examining biological responses within a chemical class.** In a separate 2024 study of published human liver-spheroid data, ScitoVation researchers found that PFAS pathway responses varied with chain length and dose⁴. The findings reinforce the importance of evaluating biological activity at the level relevant to the specific safety question rather than assuming that compounds will behave the same because they share a structural feature.

The key message is that structural similarity can provide a read-across hypothesis that can be tested with additional evidence. Transcriptomics can assess whether the proposed analogue and target compound produce concordant biological responses, while toxicokinetic analysis can determine whether differences in absorption, clearance, or internal exposure support or weaken the extrapolation. These data can therefore help establish where an analogue comparison is biologically supported, and where a more chemical-specific assessment may be warranted.

How ScitoVation helps build a defensible response

When an analogue comparison contributes to concern about a fluorinated compound, ScitoVation defines the reference compound, endpoint of concern, and evidence supporting the proposed similarity, then identifies what additional evidence can directly test the comparison.

Transcriptomic and toxicokinetic analyses can assess biological similarity and help explain apparent differences between compounds. Differences in potency, cytotoxicity, exposure duration, metabolism, or effective concentration can influence transcriptomic responses and should be considered before concluding that two compounds are biologically dissimilar.

Transcriptomics is therefore integrated as part of a comprehensive evidence package rather than standalone proof. A short-term liver-cell assay cannot, by itself, resolve environmental persistence, bioaccumulation, or all developmental, reproductive, immune, and chronic effects. Where the available model does not cover a material endpoint, that uncertainty needs to be considered through other lines of evidence.

1. **Define and test the read-across hypothesis.** ScitoVation identifies the specific comparator and endpoint driving the assessment and uses transcriptomic and toxicokinetic evidence to test whether the proposed analogue behaves similarly in biological systems and at exposures relevant to the decision.
2. **Integrate the wider evidence base.** Transcriptomic and toxicokinetic findings are considered alongside the available literature and other relevant evidence to evaluate

the scientific basis for the proposed read-across. ScitoSim™ supports this workflow by organizing evidence and supporting transcriptomic, dose-response, and biological-similarity analyses that ScitoVation scientists interpret in the context of the specific read-across question.

3. **Connect the evidence to the safety decision.** ScitoVation scientists evaluate whether the combined evidence supports the proposed extrapolation, identifies meaningful differences between the substances, or reveals uncertainties that require additional evidence.

Conclusion

Recent EPA notices show how analogue comparisons can contribute to safety assessments and regulatory decisions when substance-specific data are limited. For manufacturers of fluorinated compounds, these examples are particularly relevant because a substance may be assessed using hazard information from another chemical considered similar, including, in some cases, a PFAS analogue.

The selection of an analogue, however, is the beginning of a read-across argument, not the end. Structural similarity can provide a basis for comparison, but it does not by itself establish that two substances have comparable biological activity or toxicokinetic behavior. The scientific question is whether the similarities relevant to the particular endpoint and safety decision are supported by the available evidence. As part of the wider evidence base, transcriptomic and toxicokinetic data can help determine where a proposed read-across is biologically supported, where meaningful differences exist, and where additional evidence is needed.

Is an analogue comparison driving concern about your compound? Bring us the chemical, the proposed analogue, and the endpoint at issue. We can help determine what evidence would most directly test the comparison.

[Discuss a read-across strategy with a ScitoVation scientist.](#)

References

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