

## Background and Purpose

US EPA Office of Pollution Prevention and Toxics, New Chemicals Division (NCD), is responsible for making human health and environmental safety determinations for new chemicals submitted under the Toxic Substances Control Act (TSCA) prior to their entry into US commerce. During each new chemical human health assessment, the potential to cause skin irritation/corrosion is determined to support evaluation of chemicals by regulatory authorities. This determination has historically been performed using animal testing. As New Approach Methodologies (NAMs) have been developed and accepted by national and international entities, there has been significant work across the risk assessment community to implement NAMs into regulatory frameworks and encourage adoption by industry stakeholders. Several publications support this transition from animal (*in vivo*) studies to NAMs for evaluating skin irritation/corrosion. These publications demonstrate that NAMs provide superior reproducibility and greater biological relevance to mechanisms of human skin irritation/corrosion when compared to testing using animals, consistent with the Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program, developed by EPA in 2018 in response to TSCA section 4 (h)(2)(A) which states that EPA must:

**“develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment [...]”.**

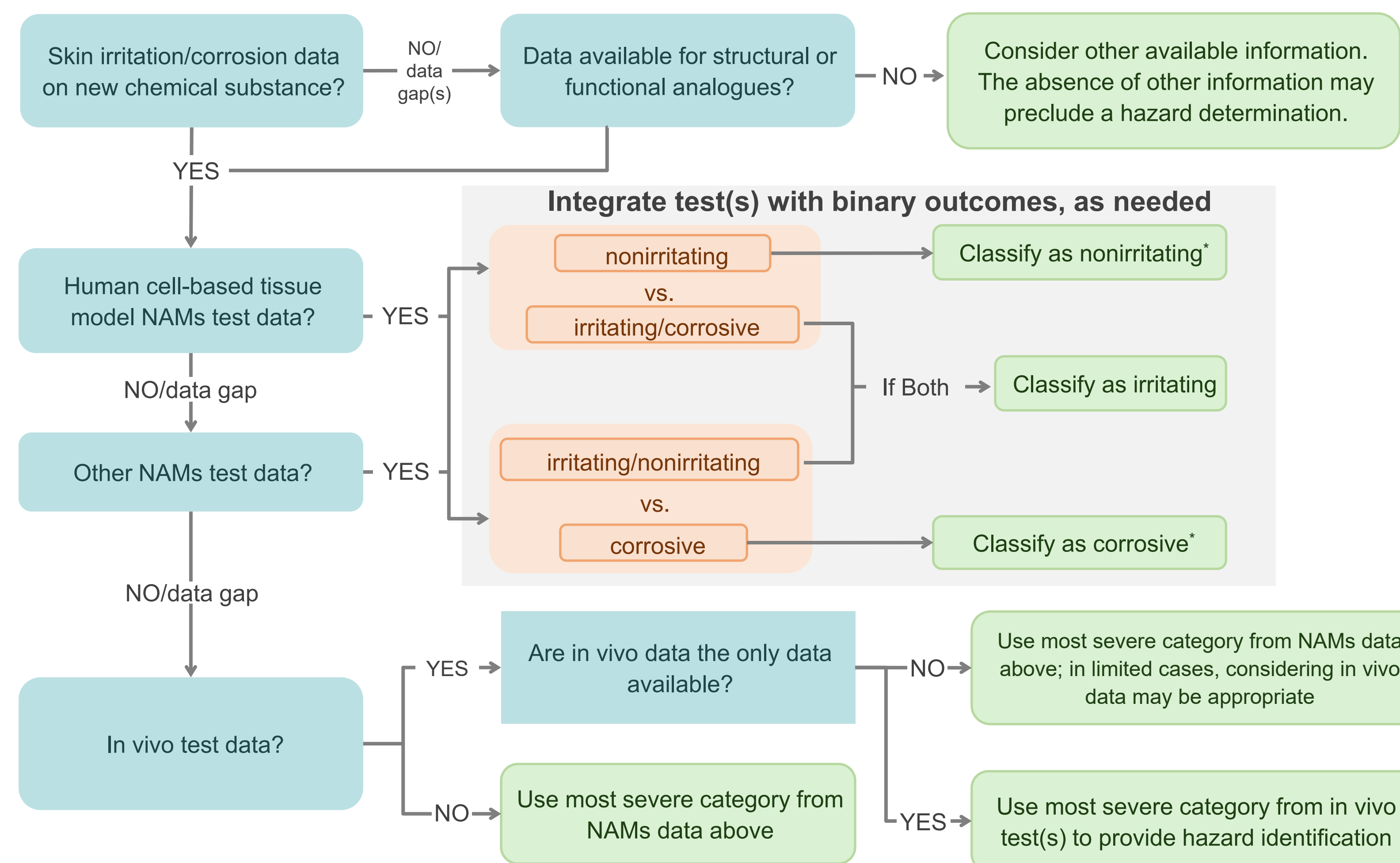
In support of this legal directive, NCD has collaborated with colleagues at PETA Science Consortium International and the Institute for In Vitro Sciences to develop an approach that prioritizes and encourages the submission of human-relevant reproducible NAMs data for the evaluation of skin irritation/corrosion for new chemicals.

## Methods

The key principle of this approach is the use of the best available science for the prediction of skin irritation/corrosion hazard in humans. Data are prioritized based on reproducibility and relevance to human skin irritation/corrosion, as follows:

1. Human cell-based tissue model NAMs
2. Other skin irritation/corrosion NAMs
3. *In vivo* test methods

## Decision Framework to Identify Skin Irritation/Corrosion based on Data Availability



Blue boxes indicate major decisions based on prioritization of data type within the framework

Orange boxes represent NAMs by hazard identification capability

Green boxes indicate outcomes.

\*In the case of conflicting data, consider additional test data and other information.

## Results

This decision framework has been implemented for assessing skin irritation/corrosion potential within NCD, including for 42 skin NAMs studies provided by submitters in 2024. The application of this framework has resulted in clear, consistent prioritization of reproducible, human-relevant data from NAMs, as well as facilitated the assessment of this hazard for new chemical substances, resulting in increased efficiency and consistency in approaches across new chemical assessments.

## Hazard Identification Capability of Some Established Test Methods

Guideline	Test Method	Hazard Classification based on Percent Tissue Viability		
<b>Human Cell-Based Tissue Model NAMs based on In Vitro Reconstructed Human Epidermis (RhE)</b>				
OECD TG 439 (Irritation)	RhE model	Nonirritating	> 50%	
		Irritating/corrosive	≤ 50%	
OECD TG 431 (Corrosion)	EpiSkin™ prediction model	Corrosive	< 35% after 3 min, OR ≥ 35% after 3 min exposure AND < 35% after 60 min, OR ≥ 35% after 60 min exposure AND < 35% after 240min	
			Irritating/nonirritating	≥ 35% after 240 min
	EpiDerm™ SkinEthic™ RHE epiCS® LabCyte EPI-MODEL24 SCT	Corrosive	< 50% after 3 min, OR ≥ 50% after 3 min AND < 15% after 60 min	
		Irritating/nonirritating	≥ 50% after 3 min AND ≥ 15% after 60 min	
<b>Other NAMs</b>				
OECD TG 435	Corrositex (in chemico)	Acid/Alkaline Reserve	High	Low
		Corrosive	≤ 240 min	≤ 60 min
		Irritating/nonirritating	> 240 min	> 60 min

## Conclusion

This approach prioritizes reproducible and human-relevant data for assessing skin irritation/corrosion potential and is expected to encourage the submission of these data from members of industry. In addition, this approach has improved the efficiency, consistency, and transparency of the assessment of skin irritation/corrosion potential within NCD. It will serve as a resource for stakeholders preparing new chemical submissions to EPA under TSCA.

## Select References

Raabe, H. A., Costin, G. E., Allen, D. G., Lowit, A., Corvaro, M., O'Dell, L., Breeden-Alemi, J., Page, K., Perron, M., Flint Silva, T., Westerink, W., Baker, E., & Sullivan, K. (2025). Human relevance of *in vivo* and *in vitro* skin irritation tests for hazard classification of pesticides. *Cutaneous and ocular toxicology*, 44(1), 1–21. <https://doi.org/10.1080/15569527.2024.2387596>

Rooney, J. P., Choksi, N. Y., Ceger, P., Daniel, A. B., Truax, J., Allen, D., & Kleinstreuer, N. (2021). Analysis of variability in the rabbit skin irritation assay. *Regul Toxicol Pharmacol*, 122, 104920. doi:10.1016/j.yrtph.2021.104920

US EPA. (2018). Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program. June 22, 2018. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention, Washington, DC. [https://www.epa.gov/sites/default/files/2018-06/documents/epa\\_alt\\_strat\\_plan\\_6-20-18\\_clean\\_final.pdf](https://www.epa.gov/sites/default/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf)