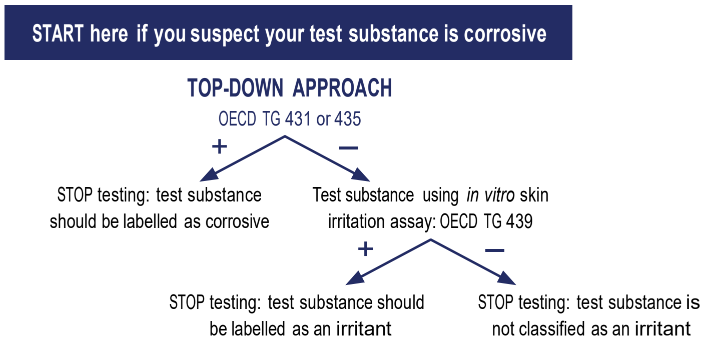
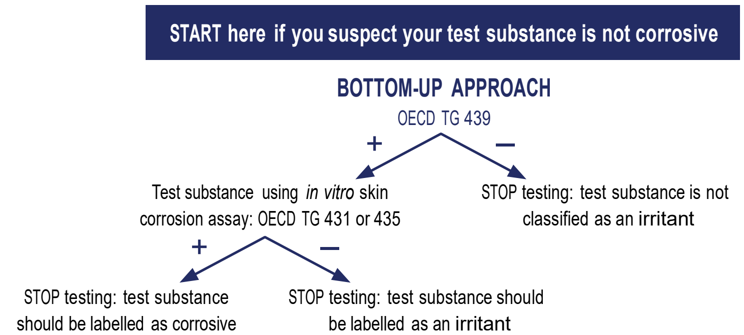
METHODS FOR PREDICTING SKIN IRRITATION AND CORROSION





METHOD	PRINCIPLE OF THE TEST	RHE MODEL (IF APPLICABLE)	APPLICABILITY DOMAIN	GHS CATEGORISATION
OECD TG 439: *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method	The test substance is applied to a three-dimensional reconstructed human epidermis (RhE) model. Following exposure and a post-exposure incubation period, the vital dye MTT is added and cell viability determined. Optional histology may also be conducted to gain further information.	• EpiDerm™ (MatTek, US) • SkinEthic™ (L'Oréal, France) • LabCyte EPI-MODEL24 (J-TEC, Japan) • epiCS® (Phenion, Germany) • Skin+™ (Sterlab, France) • KeraSkin™ SIT (Biosolution Co, Republic of Korea)	Applicable to solids, semi-solids, liquids, waxes, and mixtures.	Discriminates skin irritants (Cat 2) from substances not classified for skin irritation (No Cat). Materials that test positive should be tested for skin corrosion (bottom-up approach).
OECD TG 431: *In Vitro* Skin Corrosion: Reconstructed Human Epidermis Test Method	The test substance is applied topically to a three-dimensional RhE model. Corrosive chemicals are able to penetrate the tissue and are cytotoxic to cells in the underlying layers. Cell viability is measured using the vital dye MTT.	• EpiDerm™ (MatTek, US) • SkinEthic™ (L'Oréal, France) • epiCS® (Phenion, Germany) • LabCyte EPI-MODEL24 (J-TEC, Japan)	Applicable to solids, semi-solids, liquids, waxes, and mixtures.	Discriminates non-corrosive substances from corrosive substances (Cat 1) and allows subcategorisation into 1A or 1B and 1C together. Materials that test negative should be tested for skin irritation (top-down approach).
OECD TG 435: *In Vitro* Membrane Barrier Test Method for Skin Corrosion	The test substance is applied to the surface of an artificial membrane barrier designed to respond in a manner similar to skin *in vivo*. The time taken for the test substance to penetrate the barrier predicts corrosivity.	N/A	Applicable to solids, liquids, and emulsions. Aqueous chemicals with a pH in the range of 4.5 to 8.5 may not qualify for testing.	Discriminates non-corrosive substances from corrosive substances and allows full subcategorisation into 1A, 1B, and 1C.

Additional Reading

- Organisation for Economic Co-operation and Development. 2017. Guidance document on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation. Series on Testing and Assessment, No 203.
- European Chemicals Agency. 2017. Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific guidance. Version 6.0. See R.7.2.

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IN SILICO TOOLS FOR PREDICTING SKIN IRRITATION AND CORROSION

In silico tools can be used to assess chemicals for their potential to cause skin irritation or corrosion based on molecular structure and physicochemical properties. For example, *in silico* models can be used to predict chemical reactivity and physicochemical extremes, primary drivers of skin irritation and corrosion. The simplest *in silico* approaches involve predicting a chemical's pH, and substances with extreme pH (pH ≤ 2 or ≥ 11.5) are classified as corrosive (according to OECD and UN GHS guidelines).

Additional models include expert rule-based systems or statistical models. **Expert rule-based** systems use known structural-activity relationships (SARs) to identify specific molecular substructures known to damage skin tissue (e.g., phenols, acids, or quaternary ammonium salts). **Statistical** models, such as quantitative SARs (QSARs), correlate molecular descriptors (e.g., molecular weight, LogP, dipole moment, and/or chemical substructure) with irritation potency to distinguish between severe irritants and non-irritants.

Often, *in silico* tools are integrated into weight-of-evidence (WoE) frameworks or Integrated Approaches to Testing and Assessment (IATA). For example, a reliable *in silico* prediction of corrosion (e.g., based on pH or a rule-based system such as the Decision Support System developed by the German Federal Institute for Risk Assessment/BfR) may be sufficient to classify a chemical as GHS Category 1 (Corrosive). Conversely, an *in silico* prediction of non-irritant may be more likely to be combined with *in vitro* data to increase confidence in the prediction.

A non-exhaustive list of *in silico* tools for predicting skin irritation and corrosion is provided below. Please contact Kyle Martin at kmartin@thepsci.eu to include additional resources on this list or with any questions.

TOOL	DEVELOPER	METHOD/APPROACH	AVAILABILITY
ACD/Percepta	ACD/Labs	Statistical	Commercial
CASE Ultra	MultiCASE Inc.	Statistical	Commercial
Danish (Q)SAR Database	Danish EPA	Statistical	Open-source
Derek Nexus	Lhasa Limited	Expert rule-based	Commercial
iSafeRat	KREATiS	Statistical	Commercial
OECD QSAR Toolbox	OECD/Laboratory of Mathematical Chemistry	Statistical (read-across/QSAR)	Open-source
Toxicity Estimation Software Tool (TEST)	US EPA	Statistical	Open-source
Toxtree	IDEAconsult Ltd./European Commission	Expert rule-based	Open-source
VEGA Hub	Istituto di Ricerche Farmacologiche Mario Negri	Consensus/hybrid	Open-source