Predicting Genotoxic and Carcinogenic Risk of Pharmaceutical Impurities

According to FDA guidance for industry, impurities that are present at levels below the threshold of toxicological concern (TTC) can be evaluated for genotoxic and carcinogenic risk using computational software methods.

The Impurities Package for Toxicity was developed by ACD/Labs under the Research Collaboration Agreement with the U.S. Food & Drug Administration. The software provides a battery of in silico tests to accurately assess the genotoxic and carcinogenic potential of impurities and degradants in drug products, that can help companies remain compliant with regulatory submission requirements.

Toxicity predictions in the Impurities Package offer greater insight into the safety of impurities providing information on toxic endpoints, reflecting various mechanisms of hazardous activity including:

- Mutagenicity (Ames test, Mouse Lymphoma Assay, and other standard assays)
- Clastogenicity (Micronucleus test, Chromosomal Aberrations)
- DNA damage mechanisms (Unscheduled DNA Synthesis)
- Carcinogenicity (FDA rodent carcinogenicity data)
- Endocrine disruption mechanisms (Estrogen receptor binding)
Profile impurities using predictions for genotoxic and carcinogenic endpoints

Determine if impurity is likely to pose a safety risk and see a list of five similar structures with experimental results in relevant bioassays.

The impurities package offers probabilistic predictive models for 21 different endpoints that cover various mechanisms of hazardous activity. These predictors are supplemented with a knowledge-based expert system that identifies potentially hazardous structural fragments that could be responsible for genotoxic and/or carcinogenic activity of the compound of interest.

The expert system contains a list of 67 alerting groups of toxicophores, 53 of which account for point mutational and/or clastogenic mechanisms of DNA damage, while the remaining 14 substructures detect carcinogens acting by non-genotoxic mechanisms. The expert system was able to recognize >94% of mutagens in the ACD/Ames test database, and >90% of compounds marked as potent carcinogens in the FDA’s OFAS Food-Additive Knowledge Base database.

Learn more www.acdlabs.com/impuritiespkg

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