# 4.4: Other Approaches for Predictive Toxicity Modeling

**Learning Objectives**

- 1: Understand what Quantitative Structure Activity Relationships are and how they are used in the field of systems toxicology.

## Quantitative Structure Activity Relationships (QSAR)

QSAR models are classification models that are used to link particular structures in some molecules to causative/adverse effects at cellular/organism level. This is based on the fact that compounds that are structurally similar would have similar mechanisms of mediating toxicity. For example compounds belonging to the structural class of triazoles have been reported to cause developmental malformations such as cleft palate in rats.

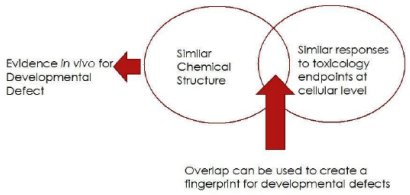
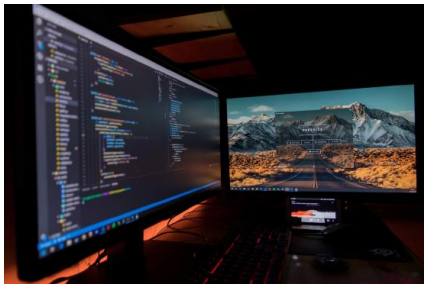



Figure 4.4.1: QSAR Approaches for Predictive Toxicity Testing

Mechanisms at the cellular level include events such as positive response for the TGFb1 signaling pathway. This information can be used to build a molecular fingerprint where compound having similar chemical structures as triazoles and having a positive response to TGFb1 signaling pathway could be flagged for potential developmental toxicity (teratogens).

## QSAR Approaches for Predictive Toxicity Testing



This method however requires a lot of data in order to build robust databases. This also requires validation of QSAR relationships with large sets of *in vitro* and *in vivo* datasets. This requires extensive collaboration between scientists across different disciplines of toxicology.

Currently, several softwares are available commercially that are used for predictive toxicology assessments. These softwares have been validated against compounds across different classes and various toxicological end points. Utilizing such tools requires detailed research and information on the extent of evaluation and validation conducted in order to develop these tools. For example softwares that have been validated with large data sets for pharmaceutical compounds may not be appropriate for using in a chemical space and vice versa.

### Names of certain commercially available Computational Tools Used In Industry

- QSAR tools: Derek, GastroPlus, ADMET Predictor, OECD QSAR Toolbox, ACD ToxSuite
- PK/PBPK Modeling Tools: GastroPlus, Simcyp, WinNonlin, Berkeley Madonna

**Topic 4: Key Points**

In this section, we explored the following main points:

- 1: The application of QSARS in systems toxicology.

**Knowledge Check**

1. QSAR databases link:

Relationship between chemical structures of compounds and their activity/toxicity

Relationship between different responses at different organizational levels

Physiologically relevant modeling tools

In vitro to in vivo extrapolation

**Answer**

Relationship between chemical structures of compounds and their activity/toxicity

2. Development of efficient QSAR tools depend on...

The user’s familiarity with the software/tool

Knowledge of multiple QSAR models

A large database of validation training sets

All of the above

**Answer**

A large database of validation training sets