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Structural alerts for the prediction of drug toxicity: a mini-review

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ABSTRACT

An essential part of drug research and development is the prediction of drug toxicity, which aims at recognizing possible hazards early on. Toxicophores, another name for structural alerts, are functional groups or molecular substructures linked to harmful biological effects. In computational toxicology, these signals are frequently used to forecast the possible toxicity of drug candidates. This mini-review explores structural alerts and their relevance in forecasting drug toxicity. We discuss the design and implementation of structural alert systems, their integration with machine learning and quantitative structure-activity relationship models, and their limitations, including the risk of over-prediction and the requirement for contextual interpretation. In addition, we discuss recent advances in the field, such as the incorporation of mechanistic insights and the use of large-scale toxicity databases. While structural alerts are still a useful technique for predicting toxicity, their effectiveness is increased when supplemented with other computational and experimental methodologies in order to provide a more thorough assessment of medication safety. This mini-review emphasizes the significance of structural alerts in guiding drug design and reducing the risk of toxicity within the preclinical development.

1. Introduction

Structural alerts are key substructures that indicate specific toxicity in compounds. They are identified through frequency analysis and statistical parameters, allowing for the prediction of toxicity by matching compounds against predefined SMARTS (SMiles ARbitrary Target Specification) patterns in the SA-predictor web-server[1]. Identifying structural alerts for toxicity involves using computational approaches like

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frequency analysis and interpretable machine learning models. These methods enhance predictive capability and can explain quantitative structure-activity relationships, aiding in both environmental toxicology and drug discovery applications[2].

Common structural alerts for toxicity include high chemical reactivity molecular fragments or those that can be bioactivated by human enzymes into reactive fragments. Approximately 78%–86% of drugs with residual toxicity contain such structural alerts, indicating their significance in drug design[3]. Structural identification faces limitations such as potential pitfalls that can lead to misleading results, scepticism about its value, and challenges in accurately correlating analytical models with measured data, which can hinder effective decision-making and performance forecasting. A limitation of structural alerts is their potential to significantly reduce the chemistry space for drug discovery, as many marketed drugs match these alerts. Additionally, strict application may overlook compounds with acceptable safety profiles, leading to missed opportunities in drug development[4].

Toxicity prediction is crucial in drug discovery as it helps filter out molecules likely to fail early in development, thereby saving time and resources. Accurate predictions enhance the efficiency of *de novo* drug design and improve overall safety in pharmaceuticals[5]. Structural alerts are key substructures predicting molecular initiating events in toxicity. They help identify chemicals' interactions with biological targets, enhancing mechanistic understanding and enabling better activity predictions through models that incorporate receptor-binding interactions and pharmacophore features[6].

Structural alerts are molecular substructures linked to mutagenic and carcinogenic properties, aiding in the classification of potential carcinogens. They help us to understand genotoxicity mechanisms, including DNA mutations, replication blockage, and interference with DNA repair processes leading to various genetic alterations. Applying structural alerts in drug discovery involves identifying substructures in drug candidates that may form reactive metabolites, which can lead to toxicity. Recognizing these alerts early can minimize the risk of adverse reactions and potential withdrawal during drug development.

Structural alerts remain a critical component of the drug discovery process, with over 50 years of established use. As research and technology continue to evolve, new techniques, such as machine learning and systems biology, will further enhance our ability to predict and mitigate toxicity, ensuring the development of safer and more effective therapeutics. An overview of the function of structural alerts in drug toxicity prediction is the goal of this mini-review. It will focus on their use in identifying molecular characteristics linked to harmful toxicological effects, such as genotoxicity, cardiotoxicity, and hepatotoxicity. This mini-review will also discuss the use of structural alerts in screening methods and computational models aiming to evaluate drug candidates' safety at an early stage of the drug discovery process. It will also point out the difficulties and restrictions associated with employing structural alerts for toxicity prediction.

2. The purposes of structural alerts

A main purpose of structural alerts is toxicity prediction by using known toxicophores (toxic structural motifs), where the structural alerts assist in identifying substances that may have mutagenic, carcinogenic, or other harmful consequences. When employed during the early screening, structural alerts lower the chances of late-stage failures by identifying potentially dangerous chemicals in the early stages of drug development. Finally, as part of the regulatory compliance, structural alerts are essential in regulating frameworks that demand toxicity evaluations for chemicals and pharmaceuticals, such as REACH and ICH M7.

3. Benefits of structural alerts

Thanks to their simplicity, structural alerts are accessible to non-experts because of their ease of interpretation and application, while due to their cost-effectiveness they offer a rapid and affordable method of screening vast chemical libraries. Moreover, the transparency of structural alerts provides understandable explanations for why a substance might be harmful, in contrast to certain machine learning algorithms[7]. Reduction of animal testing in accordance with the

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principles of 3Rs (Replacement, Reduction, and Refinement) in animal research is an additional benefit of the use of structural alerts, as the latter can lessen the need for animal testing in the early phases of drug development by providing a view of the anticipated toxicity. Structural alerts also help to advance the science of predictive toxicology as well as the standardization and knowledge-sharing by promoting cooperation and by facilitating the development of standardized toxicity databases and knowledge-sharing platforms. Finally, withstanding these advantages, it is critical to understand that structural alerts are not perfect and should be combined with additional experimental and computational methods in order to guarantee a thorough evaluation of drug toxicity.

4. Current developments

Integration with machine learning (developed by adding more chemical characteristics and context) and the combining of structural alerts with machine learning models can increase prediction accuracy. In addition to the Alert Library Expansion impart, new structural alerts for emerging toxins and underrepresented hazardous endpoints are being currently sought after. Moreover, within the Metabolism-Based Alerts, the predictive potential of structural alert frameworks is increased by integrating metabolic activation pathways[8].

5. Challenges and limitations

Using structural alerts in toxicity prediction is a common approach in computational toxicology, where specific molecular substructures or functional groups are associated with toxic effects. While this method is useful, it is characterized by several challenges and limitations.

5.1. Restricted predictive power

Although structural alerts frequently rely on well-known toxicophores or toxic functional groups, they might not fully account for the intricacies of toxicity mechanisms. Not every molecule with a structural alert is harmful, and some harmful substances might not have any known signals.

5.2. High percentage of false positives and negatives

Structural alerts may result in false negatives (in which harmful compounds are overlooked because there are no warnings) and false positives (in which non-toxic compounds are marked as toxic).

5.3. Absence of contextual information

Certain detoxification and metabolic activation processes are not taken into consideration by structural alerts. Only after undergoing metabolic change can a substance turn hazardous, something that structural alerts cannot foretell. Moreover, by ignoring biological pathways, structural alerts do not directly address toxicity, which frequently depends on interactions with biological targets (such as proteins or DNA).

5.4. Unpredictability of new toxicity mechanisms

Structural alerts are restricted to known alerts, because the structural alerts rely on past data. As a result, they might not be able to forecast toxicity for new substances or mechanisms that have not been seen before. Moreover, structural alerts might prove inadequate for complex mechanisms in which simple structural rules are insufficient to predict toxicity that results from intricate interactions or multi-step processes.

5.5. Chemical complexity and diversity

One must note that it is challenging to develop an extensive set of structural alerts due to the great diversity of chemical structures. Moreover, certain substances interact with several biological targets, thereby resulting in intricate toxicity profiles that are difficult for structural alerts to fully identify[9].

5.6. Limitations in quantitative terms

Major limitations are the absence of dose-response data (the potency and the dose-response relationship of harmful effects are not disclosed) and the binary classification undertaken without taking into account

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toxicity gradations (leading structural alerts to usually categorize chemicals as either "toxic" or "non-toxic").

6. Conclusion

By highlighting possible toxicity hazards linked to particular chemical moieties, structural alerts are useful tools that help researchers pick safer compounds and lower the possibility of adverse reactions later within the drug development process. For a more thorough and accurate evaluation of drug toxicity, structural alerts must be integrated with sophisticated computational models, *in vitro* tests, and *in vivo* studies. It is anticipated that future developments in cheminformatics, systems biology, and machine learning will improve the predictive ability of structural alerts, thereby increasing their usefulness in creating safer and more efficient treatments.

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Conflicts of interest

None exist.

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