Understanding toxicity of small molecules:

Features Identified by XAI Analysis

- Presence of a heteroatom bonded to three oxygen atoms
- Presence of a tertiary amine
- Presence of a carbon-oxygen single bond

Presence of a heteroatom bonded to three oxygen atoms:

Explanation: The presence of a heteroatom bonded to three oxygen atoms, such as in a phosphate group, is often associated with significant chemical reactivity due to the electronegative nature of oxygen atoms. This can influence the molecular structure and reactivity, potentially affecting the toxicity of small molecules.

Scientific Evidence: The document discusses the role of oxygen lone pairs in chemical reactivity, particularly in anomeric systems where oxygen atoms interact with strong sigma-acceptors (Alabugin et al., 2021). This suggests that the presence of multiple oxygen atoms bonded to a heteroatom can lead to increased reactivity and potentially influence toxicity.

Hypothesis: The presence of a heteroatom bonded to three oxygen atoms may increase the reactivity of a molecule, thereby influencing its toxicity profile due to potential interactions with biological targets.

Presence of a tertiary amine:

Explanation: Tertiary amines are known for their nucleophilic properties, which can lead to interactions with electrophilic

sites in biological systems. This can result in various biological effects, including potential toxicity.

Scientific Evidence: The SHAP analysis indicates a positive correlation between the presence of a tertiary amine and its impact on the model, suggesting its relevance in toxicity predictions (XpertAI, 2023).

Hypothesis: Tertiary amines may contribute to the toxicity of small molecules through their nucleophilic interactions with biological macromolecules, potentially leading to adverse effects.

Presence of a carbon-oxygen single bond:

Explanation: Carbon-oxygen single bonds are common in various functional groups such as alcohols and ethers. These bonds can influence the solubility, reactivity, and overall chemical behavior of a molecule, which in turn can affect its toxicity.

Scientific Evidence: The SHAP analysis shows a positive correlation between the presence of a carbon-oxygen single bond and its impact on the model, indicating its significance in toxicity predictions (XpertAI, 2023).

Hypothesis: The presence of carbon-oxygen single bonds may affect the toxicity of small molecules by altering their chemical properties, such as solubility and reactivity, which can influence their interaction with biological systems.

Summary

The analysis of features identified by XAI in relation to the toxicity of small molecules reveals several key insights. The presence of a heteroatom bonded to three oxygen atoms, such as in phosphate groups, is associated with increased chemical reactivity due to the electronegative nature of oxygen atoms,

potentially influencing toxicity (Alabugin et al., 2021). Tertiary amines, known for their nucleophilic properties, may interact with electrophilic sites in biological systems, contributing to toxicity (XpertAI, 2023). Additionally, carbon-oxygen single bonds, prevalent in functional groups like alcohols and ethers, can affect the solubility and reactivity of molecules, thereby impacting their toxicity (XpertAI, 2023). These features highlight the complex interplay between chemical structure and biological activity, underscoring the importance of understanding molecular interactions in toxicity predictions.

References

1. Alabugin, I. V., Kuhn, L., Medvedev, M. G., Krivoshchapov, N. V., Vil’, V. A., Yaremenko, I. A., Mehaffy, P., Yarie, M., Terent’ev, A. O., & Zolfigol, M. A. (2021). Stereoelectronic power of oxygen in control of chemical reactivity: the anomeric effect is not alone. *Chemical Society Reviews*.
2. XpertAI. (2024). XAI Summary.

Explanation generated with XpertAI (2024)