K206

Analysis of Twenty-eight-day Repeated Dose Toxicity Test Data in Rats Using Cascade Model

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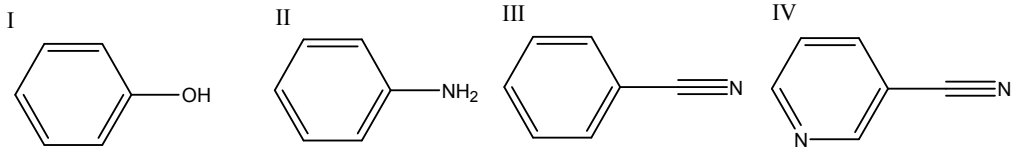
1. Introduction

The structure activity/toxicity relationship study often faces difficulty when structures of compounds are rich in variety.

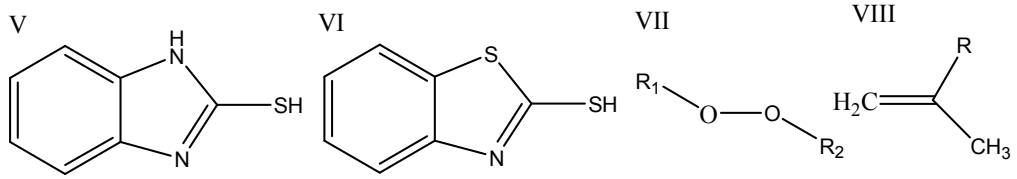
In this study, we used our data mining method, cascade model [1, 2]. We applied the method to 141 low-molecular-weight organic compounds selected from twenty-eight-day repeated dose toxicity test data in NEDO SAR project database. Here, 155 linear fragments, a part of molecular structures, were selected as descriptors. Changes of relative liver weight (RLW), GOT and GPT, adopted as toxicity indexes, were used as objective variables. We found the target toxicity was several substructures causing these toxicities.

2. Results and Discussion

RLW: Phenols I and anilines II caused increase of RLW. Among these compounds, NO_2 group increased the weight, while SO_3H group clearly suppressed the increase. A few cyanobenzene compounds III, IV also showed the increase.

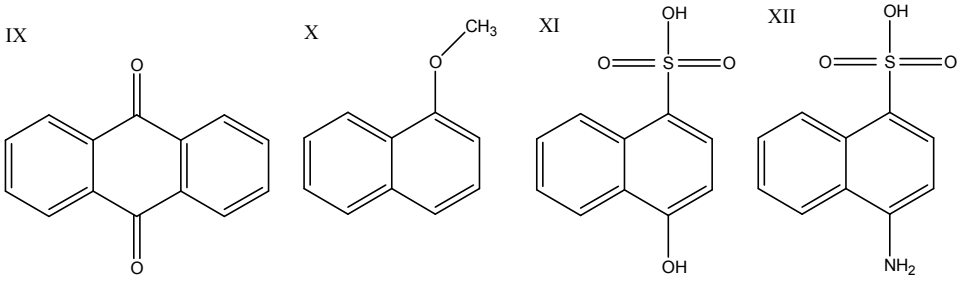


Other toxic compounds were found in benzimidazolethiol V and benzothiazolethiol VI derivatives, as well as compounds having peroxide VII and allyl substructures VIII. The radical forming character in these compounds is supposed to cause the toxicity.



A few anthraquinone compounds IX showed the increase; their effects on the redox system might be a cause. A few compounds with α,β-unsaturated carbonyl group showed the increase. Interaction with protein SH group(s) might be a cause of the toxicity.

Some compounds with high lipophilicity including naphthalene derivatives X showed the increase, but the introduction of SO_3H group brought detoxification XI, XII. Some non-aromatic compounds (methylcyclohexane, carboxylic acid esters of lipophilic alcohols, and phosphoric esters of lipophilic alcohols and phenols) showed the increase. These esters have lipophilicity and some solubility simultaneously.



There was no essential difference between male and female rats, but the latter tend to show the increase more than the former.

GOT: Numbers of Compounds affecting GOT were 21. Most of them have some characteristics found in RLW analysis. Difference in sex was larger than that in RLW.

GPT: Majority (76 %) of compounds affecting GPT showed the increase of RLW. Most of the compounds were anilines and phenols. These compounds have almost the same characteristics in terms of substructures and/or physicochemical properties as found in the RLW analysis. Difference in sex was small.

3. Conclusion

The cascade model unexpectedly led to reasonable results in spite of a small number of compounds. It was also confirmed that toxicity of compounds is closely related with their lipophilicity and reactivity. If more compounds are available from database, we will be able to present characteristic substructures causing toxicity more systematically. At the symposium we will also refer to the results on blood toxicity briefly.

Acknowledgement

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References

[1] T. Okada; in D. J. Cook and L. B. Holder eds. “Mining Graph Data”, Chap.14, Mining from Chemical Graphs, p 345-379 (2007), John Wiley & Sons, Inc.

[2] Ohmori, Fujishima, Mori, Horikawa, Yamakawa, Okada, The 36th Structure Activity Relationship Symposium, JK01(2007).