

KP213

Analysis of Repeat Dose Toxicity Test Data for Aniline Derivatives

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1. Introduction

In recent years, category approaches are extensively studied for evaluating the safety of untested chemicals based on their chemical structure. One of the most important advantages of the category approach than the other structure based estimation methods is the transparency [1].

Repeat-dose toxicity is an important endpoint that is used in many regulations such as the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) and the Japanese Chemical Substances Control Law (CSCL). However the category approach for the repeat-dose toxicity of chemicals remains to be developed.

In order to conduct category approach-based tests for determining the repeat-dose toxicity of chemicals by comparing between chemicals, it is necessary to analyze the data and histopathological findings of the test reports in detail.

Recently, we have started to analyze the 28-day repeat-dose toxicity test data for existing chemicals under Japanese CSCL in order to establish the category approach for repeat –dose toxicity data [2]. In this presentation, we report the results of the analysis on the relationship between repeat-dose toxicity and the chemical structure for aniline derivatives.

2. Method

Published reports of repeat-dose oral (gavage or feed) toxicity test conducted on rat for 20 aniline derivatives were collected mainly from National Institute of Health Science (NHIS) [3] and National Toxicology Program [4] web sites. By investigating these reports, LOELs on each target organ of male rats in each chemical are defined. Then the relationships between the feature of the chemical structure of the aniline derivatives and the defined LOELs on each target organ are investigated to categorize.

3. Results and Discussion

Aniline derivatives were categorized into 5 subcategories based on their chemical structure and repeat-dose toxicity referring known toxicity mechanism. Table 1 shows

the range of the defined LOELs on several organs for the subcategories.

Hemolytic anemia was most frequently observed findings for anilines at low dose ranges. The effect of hemolytic anemia tends to be low in the case of chemicals that are highly water soluble, such as aminophenols and aminobenzenesulfonic acids.

Table 1. Categorization of aniline derivatives based on repeat-dose oral toxicity for male rats.

| No. | Subcategory | n | Duration (day) | Max dose (mg/kg/day) | NOEL (total) | Range of LOELs for organs (mg/kg/day) | | | |
|-----|--------------------------------|---|----------------|----------------------|--------------|---------------------------------------|---------|---------|--------|
| | | | | | | Blood | Liver | Kidney | Testis |
| 1 | Anilines without a polar group | 7 | 28 | 125-360 | 1-40 | 5-250 | 10-300 | 60-360 | |
| | | 3 | 42 | 250-300 | <2-10 | 2-250 | 50-100 | 50-100 | |
| 2 | Chloroanilines | 3 | 90 | 80-160 | <5-<10 | <5-<10 | <10-80 | <5-160 | |
| 3 | Nitroanilines | 2 | 28 | 170-300 | <15-300 | 15-100 | 15-300 | 50- | 50- |
| 4 | Aminophenols | 2 | 28 | 500-720 | 20-<80 | 500-720 | 500-720 | 100-720 | |
| 5 | Aminobenzenesulfonic acids | 3 | 28 | 1000 | 300-1000 | | 1000- | | |

Fig.1 shows the relationship of the logP and LOELs on hemolytic anemia. The anilines with substituent in an ortho position tend to have low effect of hemolytic anemia in comparison with other anilines with logP>1. This is may be due to the difference in the reactivity of amino group by their position.

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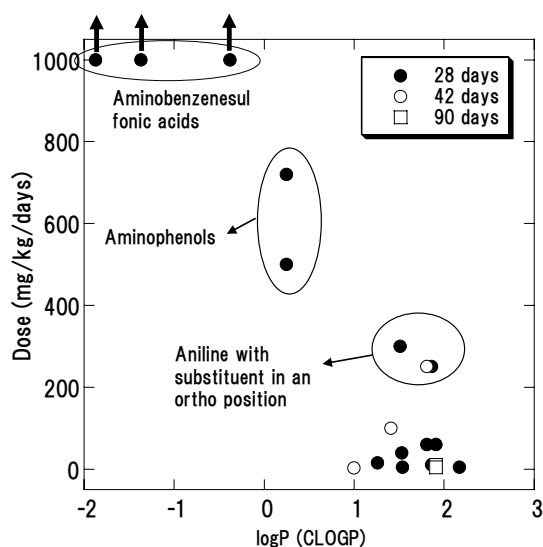


Fig. 1. logP vs LOELs on hemolytic anemia for 20 anilines.

References

1. Mekenyan O, Abstract book of The 13th International Workshop on Quantitative Structure-Activity Relationships (QSARs) in the Environmental Sciences, Syracuse, USA. (8-12 June 2008), p.20.
2. Sakuratani Y, Sato S, Nishikawa S, Yamada J, Maekawa A, Hayashi M, Abstract book of 13th International Workshop on Quantitative Structure-Activity Relationships (QSARs) in the Environmental Sciences, Syracuse, USA. (8-12 June 2008), p.11.
3. http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
4. <http://ntp.niehs.nih.gov/>