KP214 Analysis of Repeat Dose Toxicity Test Data for Nitrobenzene derivatives

Satoshi NISHIKAWA[*1], Yuki SAKURATANI[1], Sawako SATO[1], Jun YAMADA[1], Akihiko MAEKAWA[1] and Makoto HAYASHI[1,2]

1) Chemical Management Center, National Institute of Technology and Evaluation, 2-49-10, Nishihara, Shibuya-ku, Tokyo 151-0066 JAPAN

2) Biosafety Research Center, Foods, Drugs and Pesticides, 582-2, Shioshinden, Iwata, Shizuoka 473-1213 JAPAN

nishikawa-satoshi@nite.go.jp

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].

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 nitrobenzene derivatives.

2. Method

Published reports of repeat-dose oral (gavage or feed) toxicity test conducted on rat for 15 nitrobenzene 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 nitrobenzene derivatives and the defined LOELs on each target organ are investigated to categorize.

3. Results and Discussion

Nitrobenzene derivatives were categorized into 7 subcategories based on their chemical structure and repeat-dose toxicity. Table 1 shows the range of the defined LOELs on several organs for the subcategories.

Hemolytic anemia was most frequently observed findings for nitrobenzenes 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 nitrophenols and nitorobenzene sulfonic acids.

The intensity of toxicity of nitrophenols and nitrobenzenesulfonic acids for liver are also relatively low in comparison with other nitrobenzenes. This trend was similar to aniline derivatives [2].

Very similar toxicities from the histopathological findings were commonly observed for nitrobenzenes in some subcategories. These kinds of toxicities were not usually observed for anilines without nitro group.

The toxicity reported for 1,3-dinitrobenzene is also similar to this. The testis toxicity of 1,3-dinitrobenzene is thought to be induced by metabolite nitro group of the 1,3-dinitrobenzene to amino group [5]. Hence, it is likely that the testis toxicity observed in the repeat dose toxicity test for nitrobenzene derivatives were caused by nitro groups that were not metabolite to amino groups in the liver. In order to clarify this point it is necessary to compare the rate of metabolism of the nitrobenzene derivatives.

Table 1. Categorization of nitrobenzene 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	Nitrobenzene	1	42	100	<20	20	20	60	60
2	Nitrotoluenes	3	90	694-723	<45-86	165-179	42-342	82-661	353-723
3	Dichloronitrobenzenes	2	44-45	100-200	<8-5	8-25	25-40	25-200	
4	Nitrophenols	2	28	1000	160-400				
5	Nitrobenzenesulfonic acids	2	28-42	700-1000	175-300	700-	700-		
6	Nitroanilines	2	28	170-300	<15-300	15-100	15-300	50-	50-
7	Di- or tri- nitorophenols	3	28-42	7-100	<1-4	80-	80-	2-100	7-

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