RESEARCH REPORT - No. 1501 FY 2015–2016

Title of research project	Development of the new tiered approach for toxicity studies of pesticide considering species difference in "toxicity profile" and "toxicity dose-response" - evaluation of necessity of 1-year toxicity study in dogs and carcinogenicity study in mice. -
Research project no.	(1501)
Research period	FY 2015–2016
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【Abstract】

Toxicity studies required for assessment on risk of chemicals on human health differs depend on the application and the risk assessment organization. Recently, 1-year toxicity study in dogs(dog 1-year study) is not mandatory for pesticide registration in US and EU, and long-term carcinogenicity study in mice is not essential for registration of pharmaceuticals based on ICH※, but these two toxicity studies are both required for pesticide registration in Japan.

In this study, we have analyzed the data of the toxicity studies used for the risk assessment of pesticides by the Food Safety Commission of Japan（FSCJ）based on the Risk Assessment Reports, in order to propose approaches and points to be considered for scientifically evaluating the necessity of these toxicity studies in the risk assessment of pesticides.

The dog 1-year study is required in EU if there is an evidence that the dog is significantly more sensitive, and the study is required in US if bioaccumulation of the pesticide chemical is high and the elimination is so slow. 286 pesticides of which the toxicity studies were analyzed based on the risk assessment report from FSCJ, the ADI was specified based on the dog 1-year study for 93（32.5%）pesticides . By comparison of the reported NOAELs between the dog 1-year study and others, we considered that omission of the dog 1-year study has little influence on the risk assessment for 74 over 93 pesticides since the ADI values specified based on the NOAELs other than the dog 1-year study do not differ twice with the ADI based on the dog 1-year study. Moreover, the dog 1-year study was suggested to be omittable if additional detailed examinations are conducted for another four pesticides. However, the dog 1-year study seemed to be necessary to specify the appropriate ADI for the remaining 15 pesticides because dog is the most susceptible species for these pesticides. Consequently, we considered that the dog 1-year study could be omitted with only negligible influence on the current ADI in the most cases. However, the dog 1-year study should be still required or considered in proper risk assessment of pesticides in the following cases, e.g. different phenotypes are observed between dogs and rats in a subacute toxicity study, or dog seems to be most susceptible species, or pesticide have potential to accumulate by repeated administration, and in case if the dog 1-year study was already conducted, etc. It was concluded that the necessity of the dog 1-year study should be considered

carefully based on the extrapolation to human risk assessment.

On the other hands, for the assessment of carcinogenic potential of pesticides, long-term carcinogenicity study is required both in rats and mice by all of the agencies for pesticides regulation. We analyzed reports from the FSCJ on the risk assessment of 275 pesticides for which the results of rat and mouse carcinogenicity studied in both rats and mice are available, in order to evaluate necessity and usefulness of the study in mice for determining carcinogenic potential and specifying the ADI. Although 32 of 275 pesticides showed carcinogenicity in mice, the neoplastic changes observed with most of 32 pesticides were judged to be not relevant to human. Human relevance of the neoplastic changes observed with 4 pesticides could not be denied or conclusive. For 15 pesticides, the ADI was specified based on carcinogenicity study in mice, but there was no case of pesticide for which the ADI was specified based on neoplastic changes. A subacute study in mice, which is not mandatory in Japan, may be useful to evaluate the susceptibility of mice to the target pesticide. Based on the results of our analysis, we concluded that necessity and usefulness of the study in mice to determine the carcinogenic potential and to specify the ADI are not so high, and carcinogenicity study in mice may be omitted from the requirements in risk assessment of pesticides in future. However, since no agency for pesticides regulation approves the omission of carcinogenicity study in mice currently, further evaluation is necessary to clarify the conditions for the omission.

※The "ICH Guideline on Testing for Carcinogenicity of Pharmaceuticals" advocates that carcinogenicity testing of pharmaceuticals, when needed, might be carried out choosing one long-term rodent carcinogenicity study (rat) plus one other study that supplements the long-term study and providing additional information that is not readily available from the long-term study: either (1) a short- or medium-term in vivo rodent test system or (2) a long-term carcinogenicity study in a second rodent species (mouse).