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Title of research project	Establishment of interpretation on chemical induced hepatocellular hypertrophy and its future issues to be solved in risk assessment in Japan
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【Abstract】

Liver hypertrophy defined by increased weights of liver and/or hepatocellular hypertrophy is a change in the liver that commonly observed in toxicological studies of chemicals in rodents as well as dogs. Liver hypertrophy has been taxed the toxicological evaluation whether it is an early key event indicating hepatotoxicity, hepatocarcinogenicity or not. On the other hand, it is well known that hepatocyte has capacity to maintain homeostasis against stresses from both insides and outsides. This situation is accepted as beneficial adaptation. This work is performed to establish a guide for interpretation on chemical induced hepatocellular hypertrophy and its future issues to be solved in risk assessment in Japan, based on analysis of liver hypertrophy observed in toxicological evaluation data of pesticides published by Food Safety Commission, and mechanism studies in vivo and in vitro related to liver hypertrophy and extrapolation to human hazard effect. A number of informative outcomes were given from the analysis of published 252 toxicological data of pesticides. Liver hypertrophy was confirmed the most common change in the liver in rodents and dogs. The compounds showing liver hypertrophy alone were very rare, and most of compounds inducing liver hypertrophy also altered hepatotoxicity parameters including the damage to the hepatocytes, biliary ducts, lipidosis, pigmentation, or increased ALP in all species used in toxicological evaluation. Interestingly, in the comparison of inducible dose of liver hypertrophy to that of hepatotoxicity, liver hypertrophy was induced at the same dose as toxic dose or upper dose of all species in many pesticides. This result suggests that liver hypertrophy is not an early key event of hepatotoxicity. Over 40 compounds inducing liver hypertrophy simultaneously induced the thyroid effects in rodents as well as dogs. In the mechanism studies in vivo and in vitro related to liver hypertrophy and extrapolation to human hazard effect, important evidence to put into the guide of interpretation of liver hypertrophy was provided. In the in vivo studies of triazole, or other pesticides, which are inducible liver hypertrophy, using constitutive androstane receptor knockout (CARKO) mice, liver hypertrophy was not considered an early key event for hepatocarcinogenesis whereas CAR played important roles for hepatocarcinogenesis. Liver hypertrophy might be associating event, but not essential for liver tumor development. Other in vivo study using mice, PXR related liver hypertrophy by pyperonylbutoxide was strain specific. Several in vitro studies have been progressing. On the basis of the results obtained for 2 years, we established interpretation on chemical induced hepatocellular hypertrophy and its future issues to be solved in risk assessment in Japan and submitted to a reviewed scientific journal. The article was accepted and will be published April this year. In brief, the article describes about a scientific principle for determining whether liver hypertrophy, a common change in the liver induced by xenobiotics in toxicological studies, is an adaptive

or adverse event. To maintain homeostasis in the whole organism, the liver hypertrophy (hepatocellular hypertrophy and increased relative liver weight) frequently responds to xenobiotic exposure by increasing metabolic capacity via nuclear receptor activation. Such hepatic adaptive responses are potentially beneficial in the increased capacity of the organism to respond to chemical-induced stress. However, they have limits to these homeostatic responses, and exceeding status over these limits should be recognized as adverse. Practically, hepatocellular hypertrophy with following alterations should be a starting point to be considered adverse:1) hepatocellular degeneration/necrosis and/or accompanying with inflammatory reaction, 2) changes indicating damage to biliary tracts, 3) disruption of fat metabolism, 4) pigmentation, 5) deviation from typical localization or morphologic features of hypertrophied hepatocytes. This interpretation was collabolating work with Prof. Koichi Yoshinari, Shizuoka School of Pharmaceutical Sciences, University of Shizuoka, and his colleagues.