Reproducibility and variance of liver effects in subchronic and chronic repeat dose toxicity studies

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In vivo studies provide reference data to evaluate alternative methods for predicting toxicity. However, the reproducibility and variance of effects observed across multiple *in vivo* studies is not well understood. The US EPA's Toxicity Reference Database (ToxRefDB) stores data from EPA guideline studies including subchronic (SUB) and chronic (CHR) studies. The current work focused on the reproducibility of liver effects in SUB and CHR studies, as evaluation of liver weight, gross and micropathology are required by guideline. The objectives of this work include determination of: (1) the probability that liver effects were observed in replicate SUB or CHR studies; (2) the variance in observed liver effects in SUB and CHR studies; and, (3) the potential for prediction of CHR liver effects from SUB studies. Liver effect reproducibility was evaluated for chemicals with >1 SUB or >1 CHR study, and the percent of CHR or SUB studies with liver effects was determined for each chemical. For chemicals with liver effects in replicate SUB or CHR studies, multi-linear regression and analysis of variance were used to quantify the total variance in the low effect levels (LELs) and the fraction attributable to study parameters (strain, dose-spacing, etc). Replicate SUB (216 chemical; 532 studies) and CHR (366 chemicals; 956 studies) studies demonstrated 71% and 64% concordance, respectively, where concordance was defined as 100% presence or absence of any liver effect for all SUB or CHR studies by chemical. The total variance in liver effects was ~ 0.79 log10 (LEL) for SUB (135 chemicals; 328 studies) and ~ 0.86 log10 (LEL) for CHR studies (210 chemicals; 528 studies); for both SUB and CHR, approximately one-third of the variance could not be attributed to study parameters. Of the 161 chemicals with both SUB and CHR studies, 80 chemicals demonstrated concordance at the study level, i.e. agreement in response among SUB and among CHR. Of these 80, 53 chemicals demonstrated liver effects in both SUB and CHR, 15 showed no liver effects in either SUB and CHR, and 12 were discordant between SUB and CHR. Given this quantification of concordance within SUB and CHR studies, and the variance in observed effects, the upper bounds for confidence intervals around predictions of liver toxicity as well as prediction of liver effects from SUB to CHR studies can be defined. *This abstract does not necessarily reflect U.S. EPA policy.*