

How should hepatocellular hypertrophy, enzyme induction and liver weight increases be interpreted in toxicological studies in rodents?

Agreed at WG-IV-2018 on 4 July 2018.

Liver cell hypertrophy and liver weight increase should be considered as potentially adverse effects. However, on a case-by-case basis, hepatocellular hypertrophy leading to $\leq 15\%$ increased mean absolute or relative liver weight, should not be regarded as adverse, and should not be used for the purpose of defining the LOAEL for that specific study, in the demonstrated absence of all of the following changes:

- other histopathological findings such as necrosis, inflammation, fibrosis, vacuolation, pigmentation, degeneration, hyperplasia, etc. but not limited to these,
- other effects that are indicative of specific liver toxicity, such as adverse clinical chemistry changes.

If relevant and comprehensive histopathological and clinical-chemistry investigations have not been performed or where there is insufficient information to determine whether the observed increase in liver weight is an adaptive or an adverse response, then the default is to assume that the effect is adverse. Mechanistic information such as enzyme induction can be used to support decision making.

Further information was provided by UK in an annex that was not endorsed as such, but the Human Health WG generally agreed with the principles presented therein. This non-endorsed annex is available in S-CIRCABC: https://webgate.ec.europa.eu/s-circabc/d/a/workspace/SpacesStore/3733c8dc-419c-4c58-ad1c-af18c4f333af/Interpretation%20of%20liver%20effects_annex.pdf