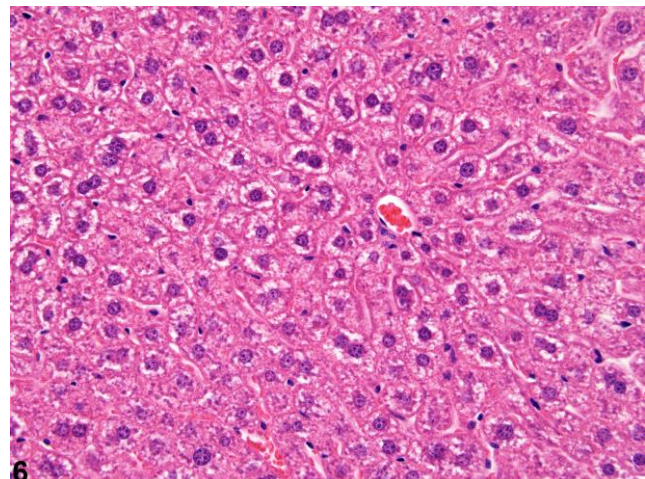
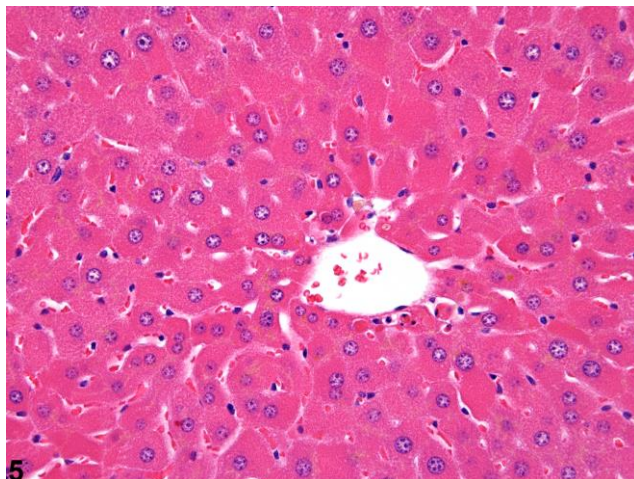
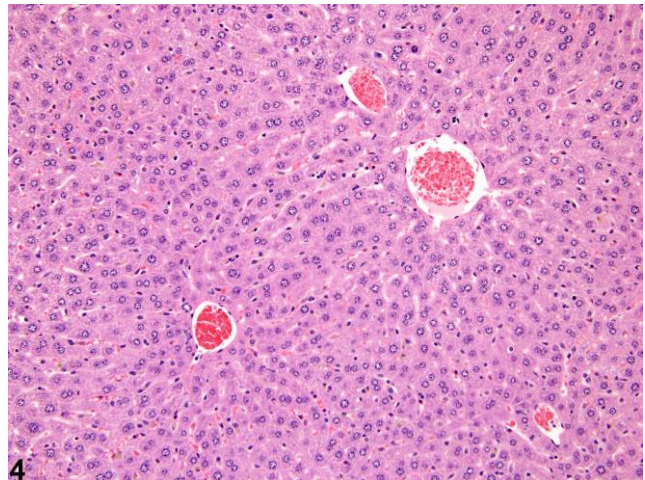
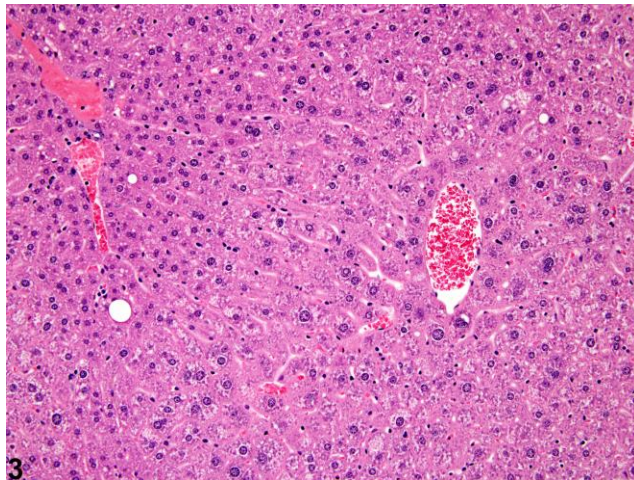
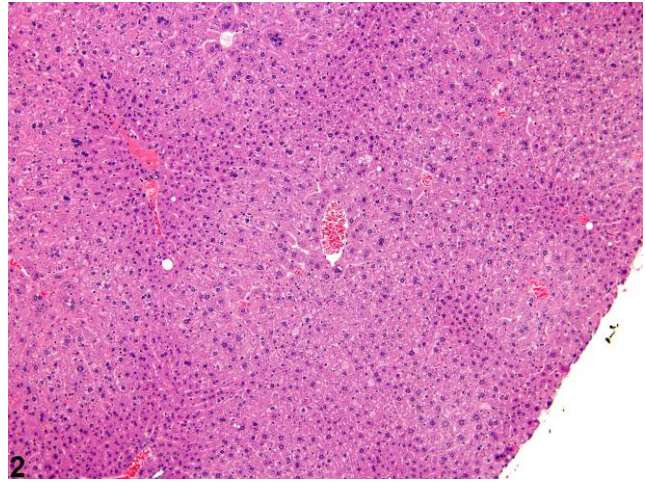
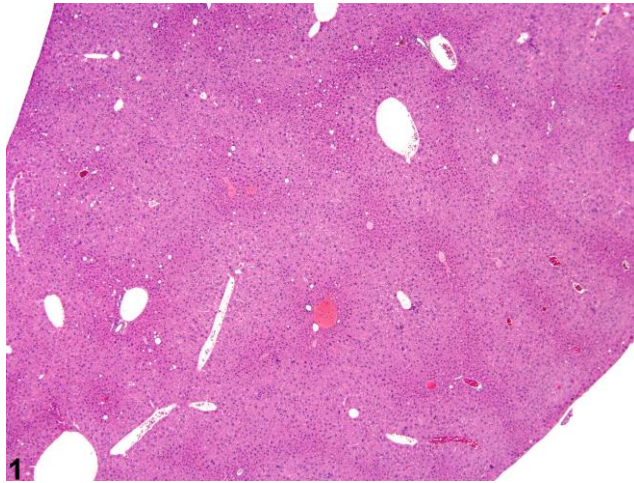




NTP Nonneoplastic Lesion Atlas

Liver, Hepatocyte – Hypertrophy





NTP Nonneoplastic Lesion Atlas

Liver, Hepatocyte – Hypertrophy

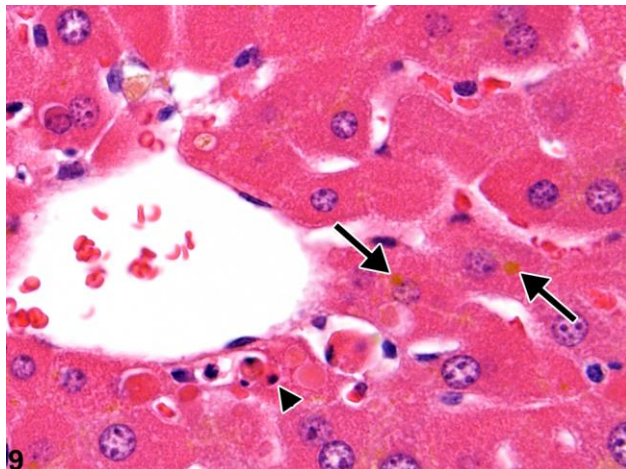
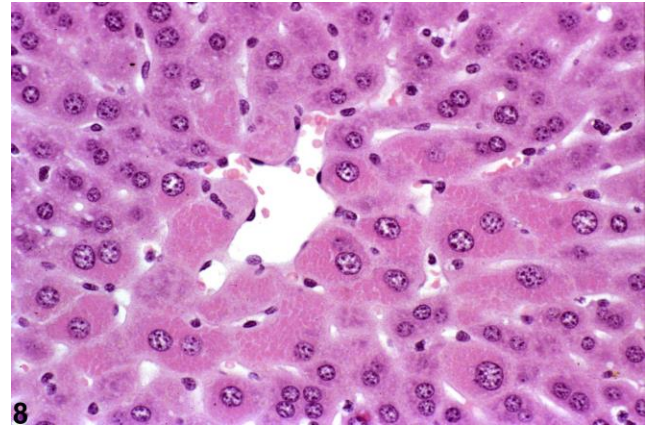
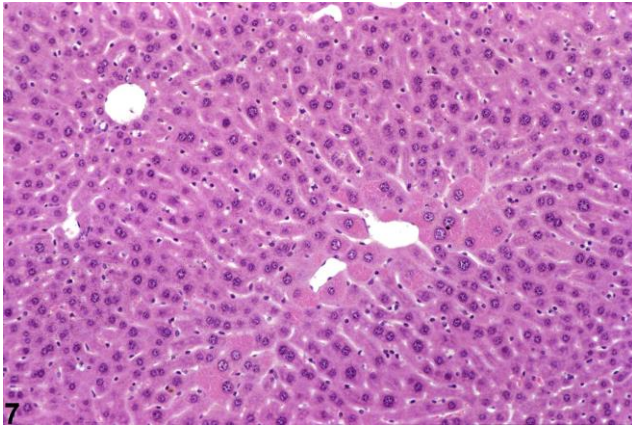
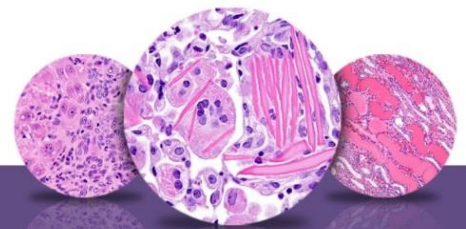


Figure Legend: **Figure 1** Hepatocyte hypertrophy in a male B6C3F1 mouse from a chronic study. **Figure 2** Hepatocyte hypertrophy in a male B6C3F1 mouse from a chronic study. **Figure 3** Hepatocyte hypertrophy in a male B6C3F1 mouse from a chronic study. **Figure 4** Normal liver in a male B6C3F1 mouse from a subchronic study, age and sex matched for comparison with Figure 3. **Figure 5** Hepatocyte hypertrophy in a male B6C3F1 mouse from a subchronic study. **Figure 6** Normal liver in a male B6C3F1 mouse from a subchronic study, age and sex matched for comparison with Figure 5. **Figure 7** Hepatocyte hypertrophy in a male B6C3F1 mouse from chronic study. **Figure 8** Hepatocyte hypertrophy in a male B6C3F1 mouse from chronic study. **Figure 9** Hepatocyte hypertrophy—arrows indicate retention of bile pigment, and arrowhead indicates apoptotic hepatocytes, in a male B6C3F1 mouse from a subchronic study.



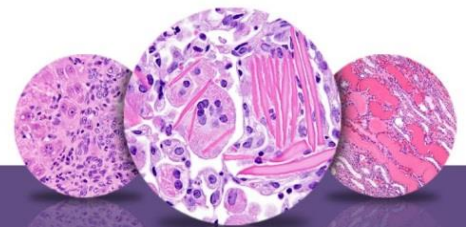
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Liver, Hepatocyte – Hypertrophy

Comment: Hepatocyte hypertrophy is a form of cytologic alteration that is diagnosed based on an observable increased size of hepatocytes compared with concurrent control liver. It is most readily apparent when it has the commonly occurring centrilobular distribution pattern; when it is panlobular, comparison with concurrent controls can provide diagnostic confirmation. When mild, detection of hepatocyte hypertrophy may be difficult, but its identification is facilitated at low magnification.

Hepatocyte hypertrophy is commonly associated with microsomal enzyme induction secondary to exposure to certain xenobiotics (Figure 1, Figure 2, and Figure 3). It most frequently affects centrilobular hepatocytes, depending upon the xenobiotic and the dose administered, although the hypertrophy can extend into the middle of the hepatic lobule or become panlobular. It is also possible for periportal hepatocytes to be primarily affected, though care must be taken not to confuse periportal hypertrophy with processes that result in shrinkage of centrilobular hepatocytes (e.g., glycogen depletion). Figure 4 is a normal control liver from the same study for comparison with Figure 3. Depending upon the specific xenobiotic responsible, hypertrophic hepatocyte cytoplasm may have a pale, ground glass appearance or be granular and intensely eosinophilic, especially following exposure to peroxisome proliferators (Figure 5). Figure 6 is a concurrent control liver for comparison with Figure 5. Marked hypertrophy with associated karyomegaly and multinucleated hepatocytes may be seen with chronic exposure to some nongenotoxic hepatic toxicants.

A narrow centrilobular zone of hepatocyte hypertrophy is present in Figure 7 (higher magnification in Figure 8). The finely granular eosinophilic cytoplasm in the enlarged hepatocytes is similar to that seen with peroxisome proliferation, but in this case the cytologic alteration responsible for the hepatocyte hypertrophy was considered hyaline change. In extreme forms, hyaline change can form distinct cytoplasmic inclusions, sometimes referred to as Mallory bodies. Figure 9 is a high magnification of the central vein area of Figure 5 and shows apoptosis of hepatocytes (arrowhead) and retention of bile pigment (arrows). Hepatocyte degeneration and cell death can occur because of reduced blood flow secondary to sinusoidal compression by enlarged hepatocytes.



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Liver, Hepatocyte – Hypertrophy

Recommendation: Hepatocyte hypertrophy should be diagnosed and graded whenever present. Subtle cases may be difficult to diagnose, and in many instances, comparison with concurrent controls is necessary to confirm the diagnosis. If hypertrophy is suspected but not clear-cut, then a blind evaluation of the slides comparing the relevant dose groups with controls is appropriate. Accompanying increases in liver weight may provide some comfort in diagnosis when the change is marginal. When possible, the diagnosis of hepatocyte hypertrophy should be qualified with a distribution pattern and given a qualitative severity grade. If the hepatocytes are enlarged due to the presence of cytoplasmic vacuoles or inclusions, hypertrophy should not be diagnosed; rather, the cytoplasmic vacuolization or cytoplasmic inclusions should be recorded, unless there is other, definitive evidence of hypertrophy.

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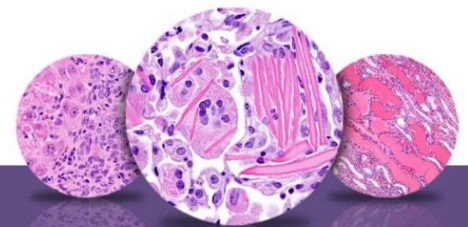
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