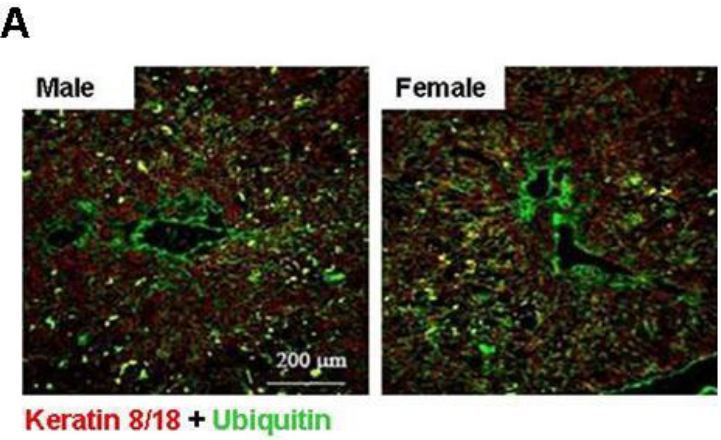
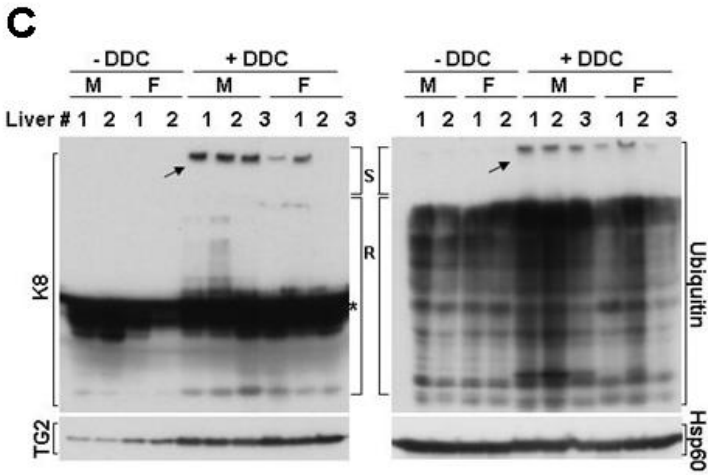
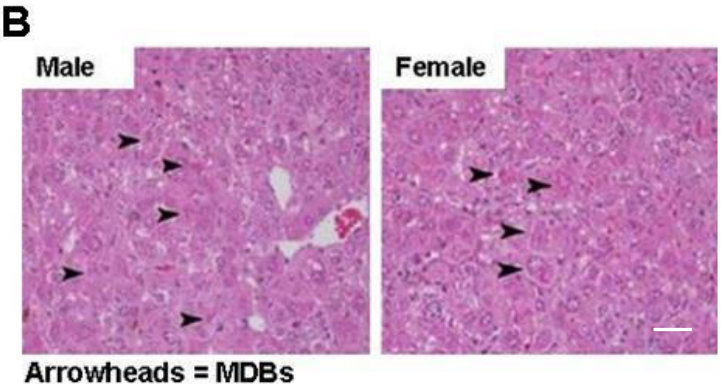
Supplementary Table 1 Primer sequences used for quantitative real-time PCR.

Gene	Primer
L7	F: GAAAGGCAAGGAGGAAGCTCATCT R: AATCTCAGTGCGGTACATCTGCCT
mouse K8	F: GGACATCGAGATCACCACCT R: TGAAGCCAGGGCTAGTGAGT
mouse K18	F: CAAGTCTGCCGAAATCAGGGAC R: TCCAAGTTGATGTTCTGGTTTT
p62	F: AGCTGCCCTCAGCCCTCTA R: GGCTTCTCTTCCCTCCATGTT







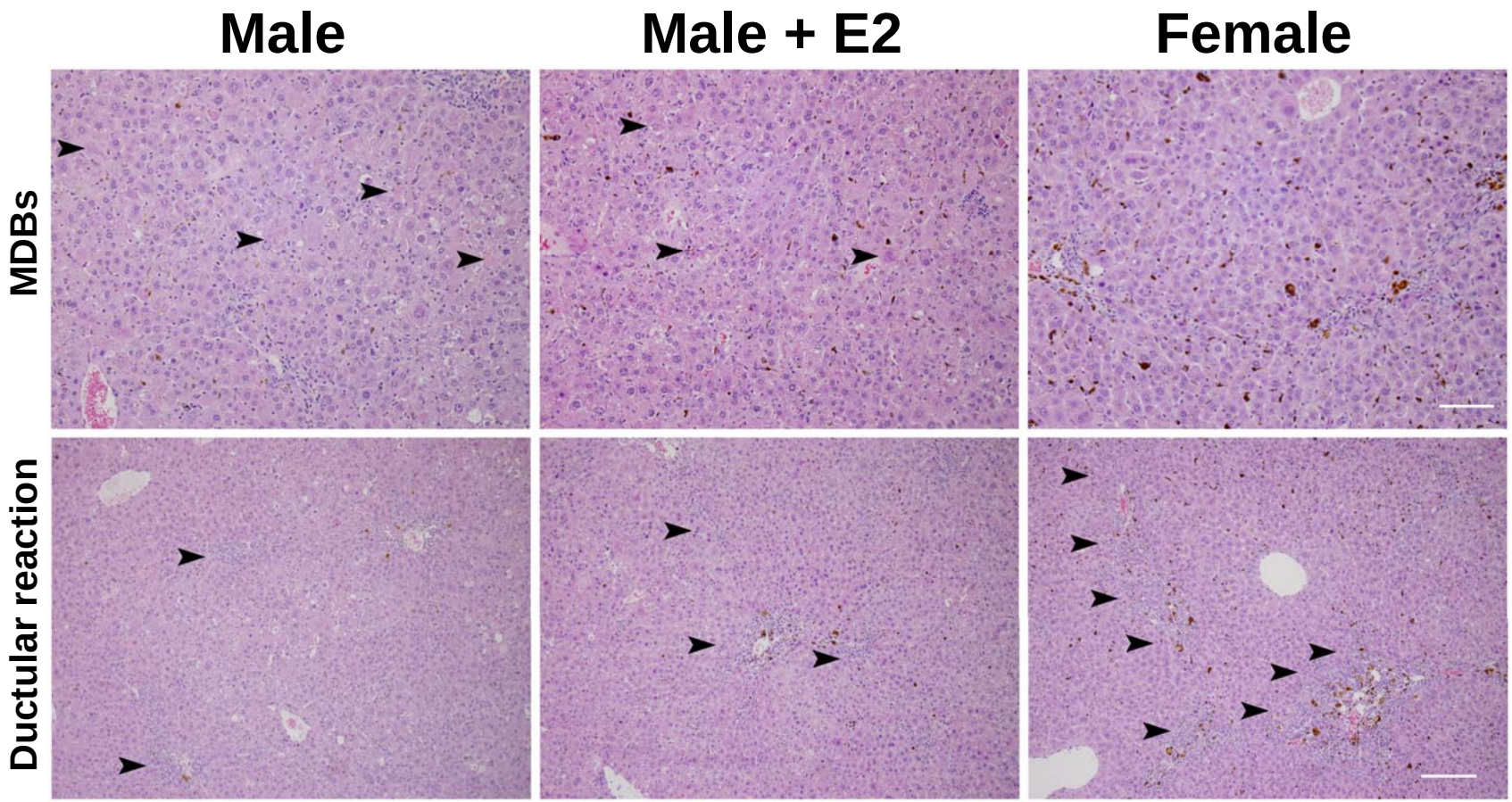
D

# of MDBs

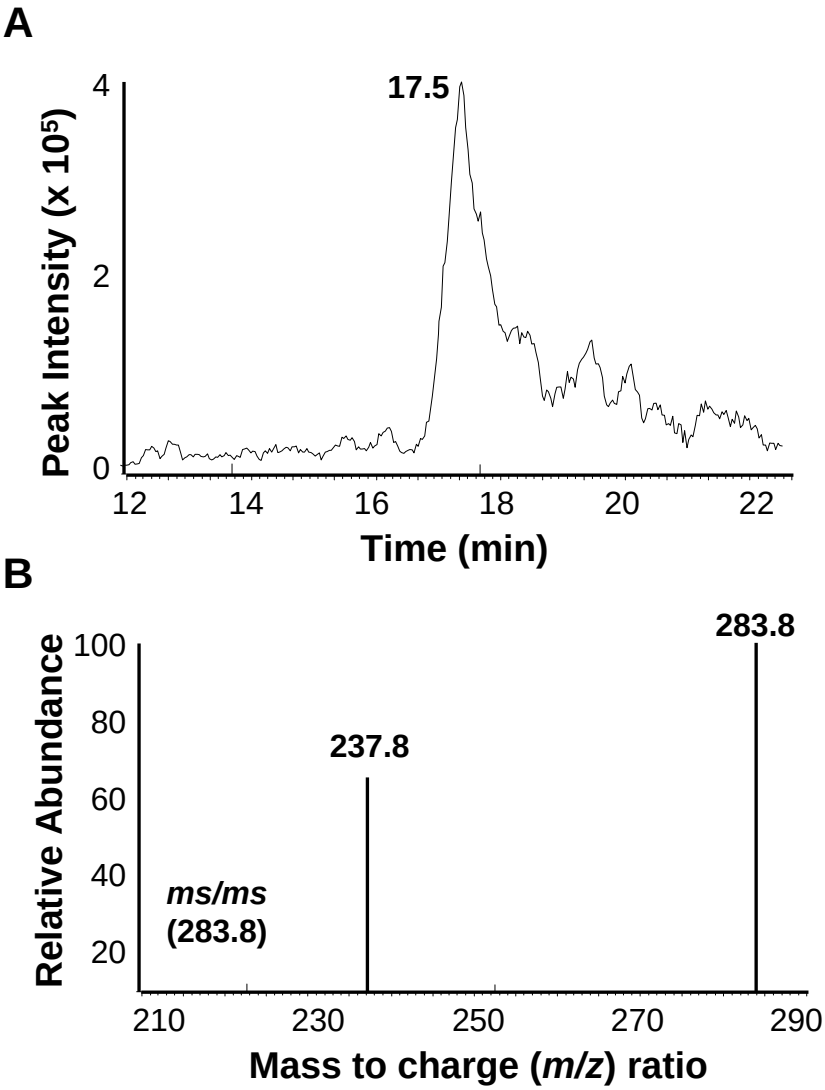
	Male (n=5)	Female (n=5)
H&E	22.7±13.2*	13.3±11.9*
FL	125.2±19**	68.8±19.4**

*P<0.01, **P<0.05

Supplementary Figure 1 Gender dimorphic formation of Mallory-Denk Bodies (MDBs) in the livers of mouse K8-overexpressing mice. (A) MDB detection by immunofluorescence (FL) staining of K8/K18 (red) and Ub (green) in male and female mice fed DDC for 90 days (scale bar represents 200 μm). (B) Routine histological analysis for the presence of MDBs (scale bar represents 100 μm) (C) Biochemical analysis for the presence of high molecular weight K8 and Ub-containing complexes (arrows) in stacking gels (S), K8 monomer and Ub conjugates in resolving gels (R), and expression of TG2 and Hsp60 in control and DDC-fed male and female mice (D) Quantitative assessment of MDB formation by FL and H&E analysis



Supplementary Figure 2 Histological analysis for the presence of Mallory-Denk bodies (MDBs) and ductular reaction in the livers of male, female, and estradiol (E2)-treated male FVB/N mice fed DDC for 90 days. Top three panels show MDBs (scale bar represents 100 μm) and bottom three panels show ductular reaction (scale bar represents 250 μm), each denoted by the arrowheads.



Supplementary Figure 3 Metabolism of DDC by human recombinant CYP3A4. **(A)** Formation of a monooxygenated DDC product (*m/z* 283.8; retention time 17.54 min) upon incubation of DDC with human recombinant CYP3A4 in the presence of NADPH, as described in Materials and Methods. **(B)** Tandem MS of the DDC metabolite showing the precursor ion (*m/z* 283.8) and a fragment ion (*m/z* 237.8; loss of CH3CH2OH).