## Supporting Information

# Gender-Dependent Reproductive Toxicity of Copper Metal-Organic Frameworks and Attenuation by Surface Modification

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**Figure S1-S19**

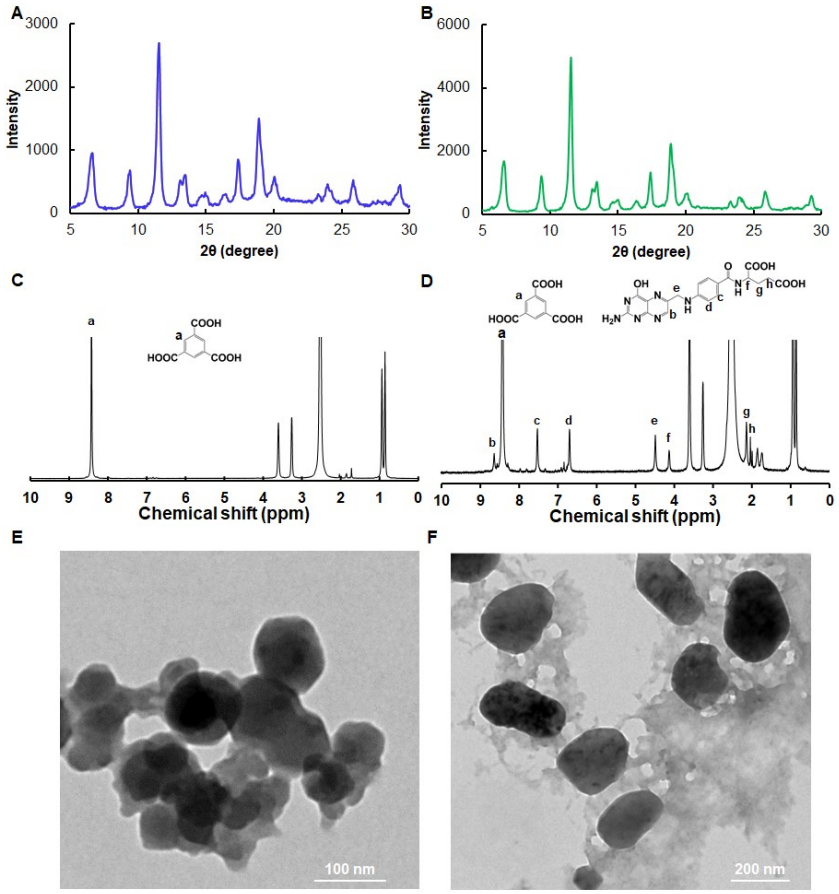


**Figure S1.** The characterization of copper MOFs. (A, B) PXRD patterns of (A) HKUST-1 and (B) F-HKUST-1. (C, D) $^{1}$H NMR of (C) HKUST-1 and (D) F-HKUST-1 dissolved in DMSO-$d_6$/$D_2SO_4$ (9:1, v/v). (E, F) TEM images of (E) HKUST-1 and (F) F-HKUST-1.

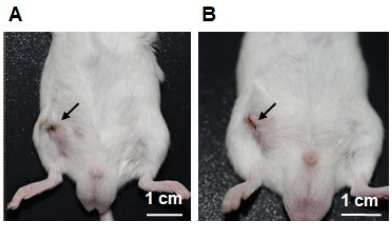


**Figure S2.** Photographs of damaged groin tissues after injection of (A) HKUST-1 or (B) F-HKUST-1 at 8.28 μmol/mouse for 10 times in 30 days. Arrows point to the damaged sites.

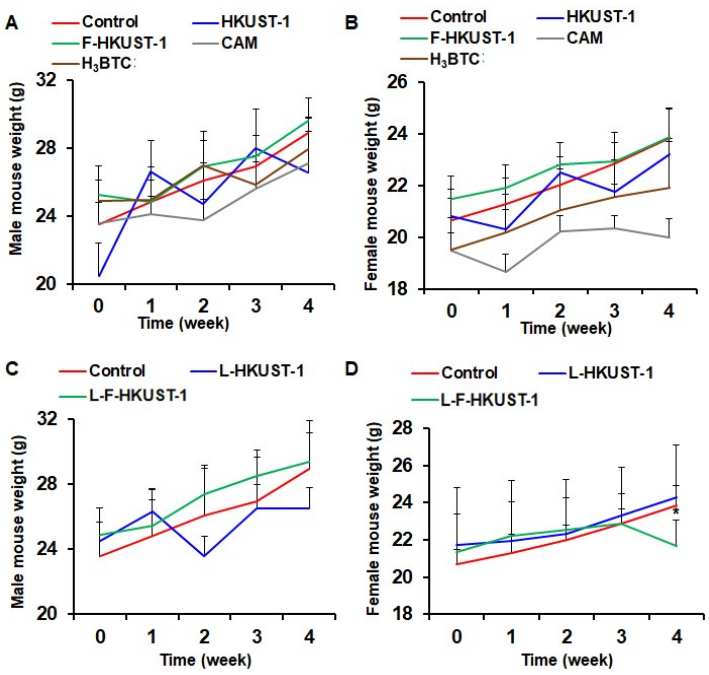


**Figure S3.** Mouse body weight trends in treatment periods. Body weight changes of (A, C) male or (B, D) female mouse after exposure with CAM, $H_3BTC$, HKUST-1, or F-HKUST-1, at (A, B) 0.92 μmol/mouse or (C, D) 0.10 μmol/mouse. L-HKUST-1 and L-F-HKUST-1 represent HKUST-1 and F-HKUST-1 at lower dose, respectively. (6 mice for each group, $^{*}P < 0.05$).

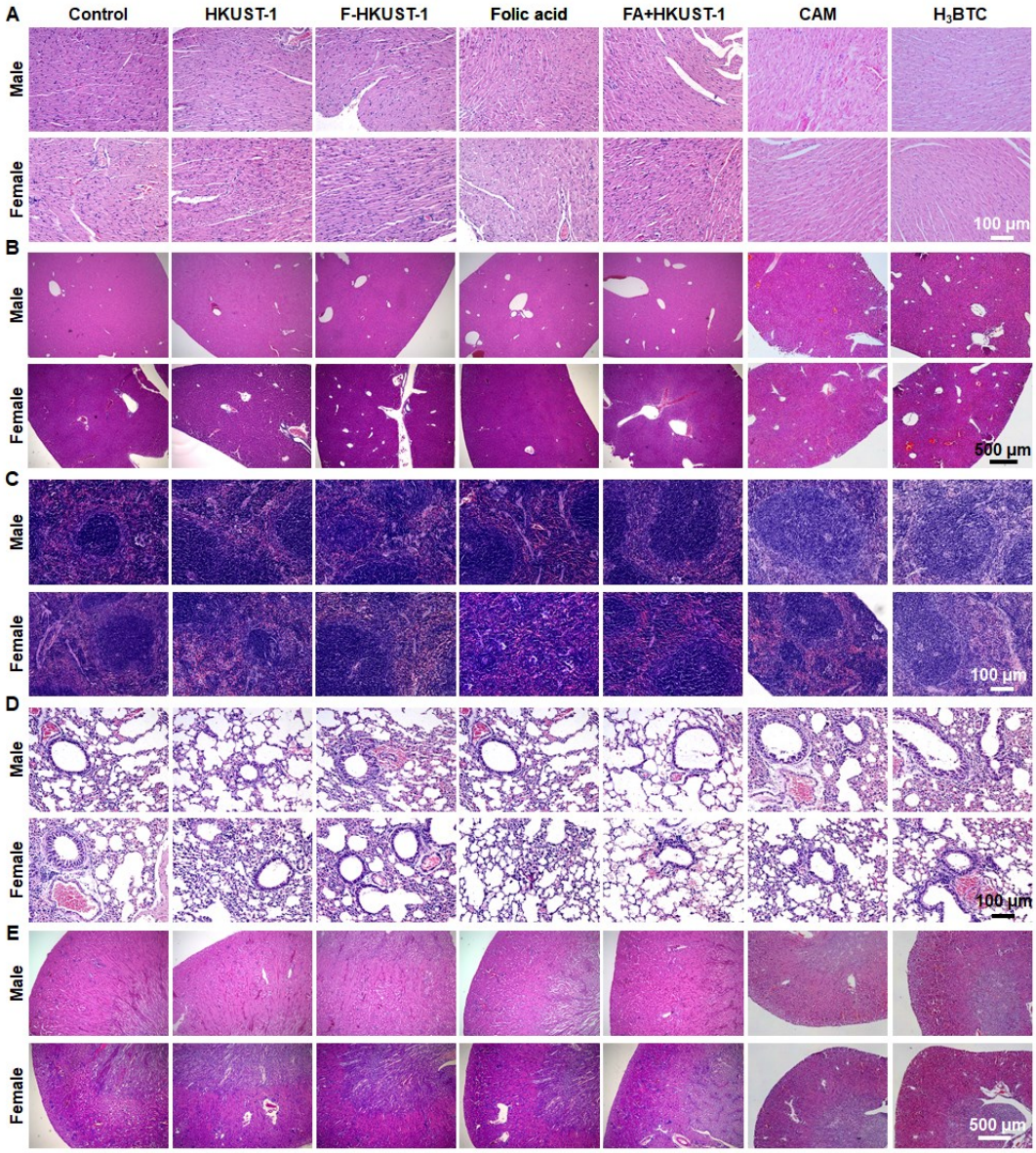


**Figure S4.** The effects of CAM, $H_3BTC$, or copper MOFs on main tissues. H&E photographs of (A) heart, (B) liver, (C) spleen, (D) lung, and (E) kidney after male or female mice were treated with CAM, $H_3BTC$, or copper MOFs for 10 treatments at dose of 0.92 μmol/mouse.

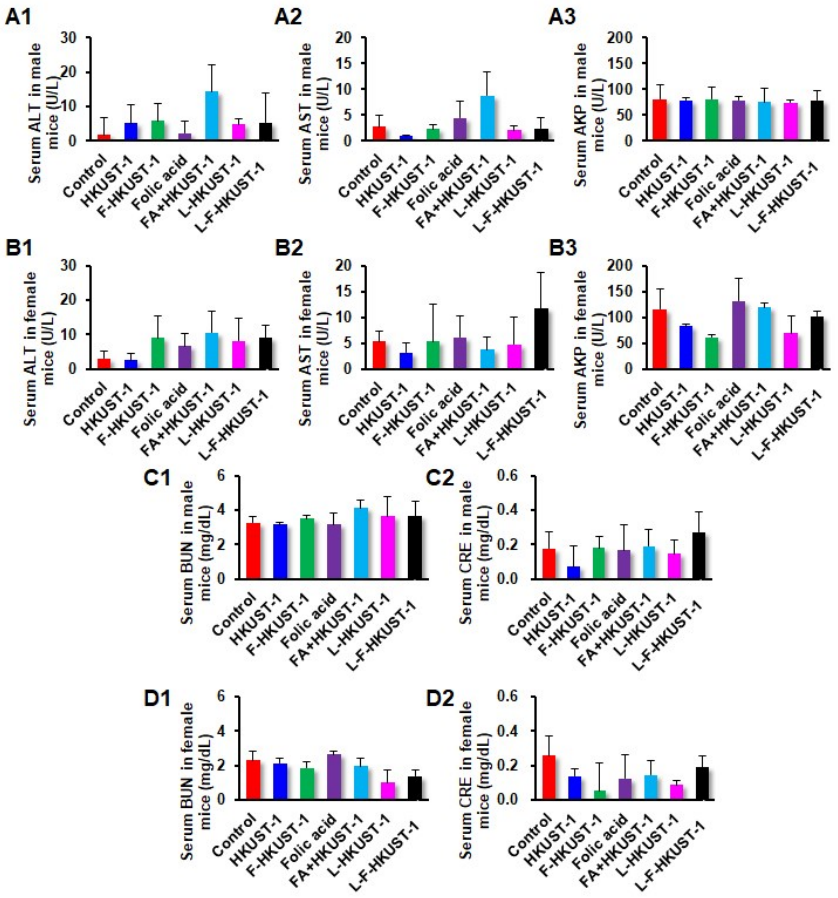


**Figure S5.** The effects of copper MOFs on liver and kidney functions. Mice were administered with HKUST-1 or F-HKUST-1 every 3 days for total 30 days at the dose of 0.92 or 0.10 μmol/mouse, the blood was collected and the serum levels of ALT, AST, AKP, BUN, and CRE were determined following the manufacture's protocols. (A1-A3) Serum levels of (A1) ALT, (A2) AST, (A3) AKP in male mice. (B1-B3) Serum levels of (B1) ALT, (B2) AST, (B3) AKP in female mice. (C1, C2) Serum levels of (C1) BUN, (C2) CRE in male mice. (D1, D2) Serum levels of (D1) BUN, (D2) CRE in female mice. L-HKUST-1 and L-F-HKUST-1 represent HKUST-1 and F-HKUST-1 at lower dose, respectively. (3 mice for each group)

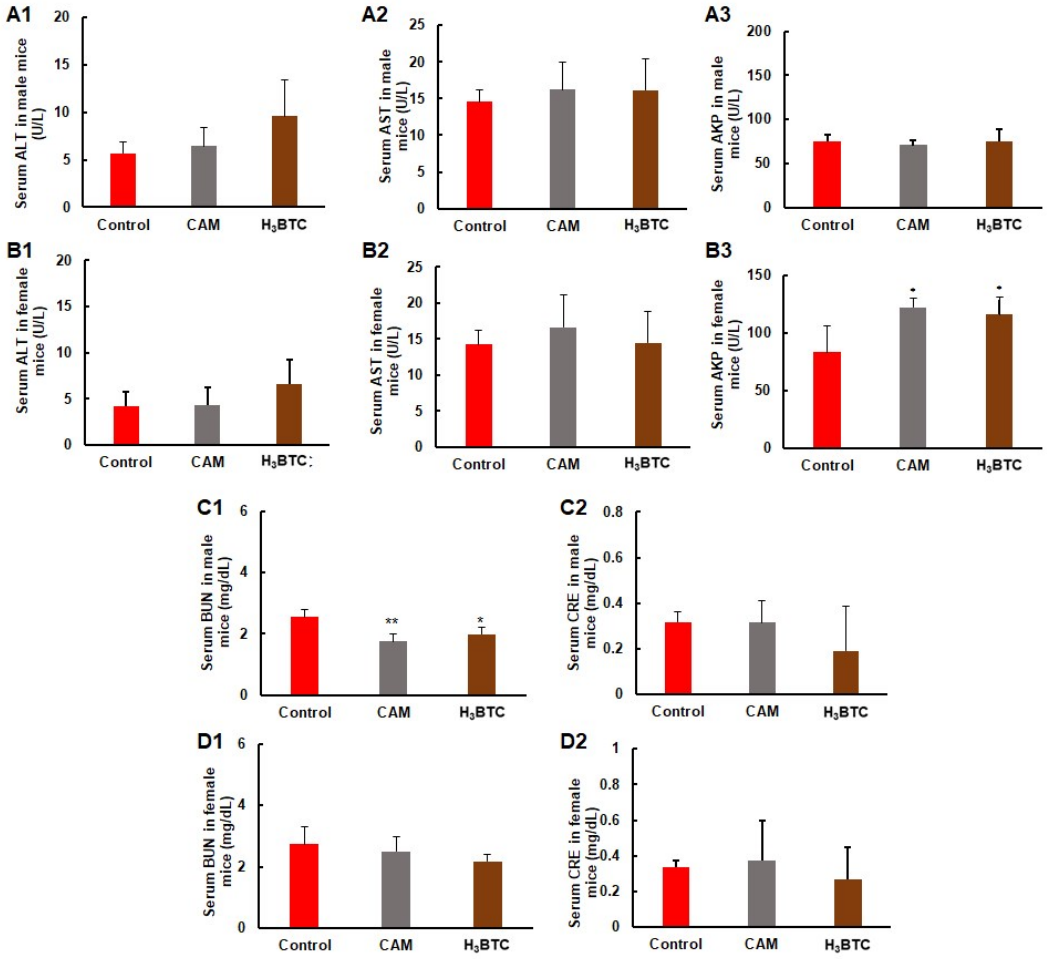


**Figure S6.** The effects of CAM and $H_3BTC$ on liver and kidney functions. Mice were administered with CAM or $H_3BTC$ every 3 days for total 30 days (CAM: 0.92 μmol/mouse; $H_3BTC$: 0.61 μmol/mouse), the blood was collected and the serum levels of ALT, AST, AKP, BUN, and CRE were determined following the manufacture's protocols. (A1-A3) Serum levels of (A1) ALT, (A2) AST, (A3) AKP in male mice. (B1-B3) Serum levels of (B1) ALT, (B2) AST, (B3) AKP in female mice. (C1, C2) Serum levels of (C1) BUN, (C2) CRE in male mice. (D1, D2) Serum levels of (D1) BUN, (D2) CRE in female mice. (6 mice for each group)

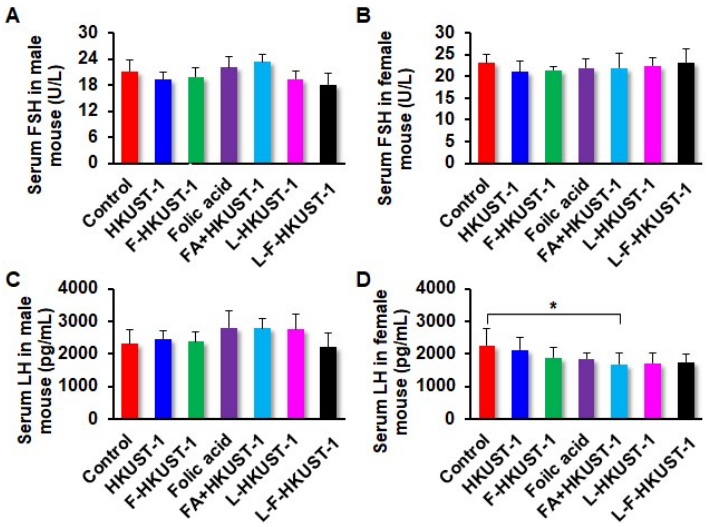


**Figure S7.** Sex hormone levels in mice with copper MOF exposures. (A, B) FSH levels in (A) male or (B) female mice. (C, D) LH level in (C) male or (D) female mice. L-HKUST-1 and L-F-HKUST-1 represent HKUST-1 and F-HKUST-1 at lower dose, respectively. (6 mice for each group, $^{*}P < 0.05$)

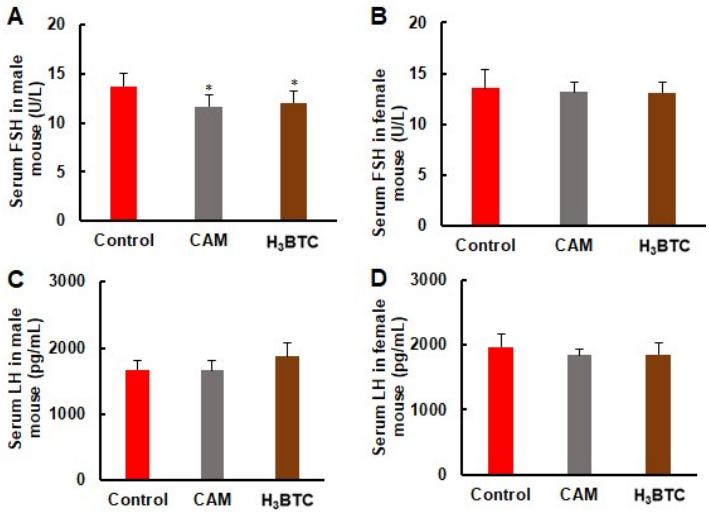


**Figure S8.** Sex hormone levels in mice with CAM or $H_3BTC$ exposures. (A, B) FSH levels in (A) male or (B) female mice. (C, D) LH level in (C) male or (D) female mice. (6 mice for each group, $^{*}P < 0.05$)

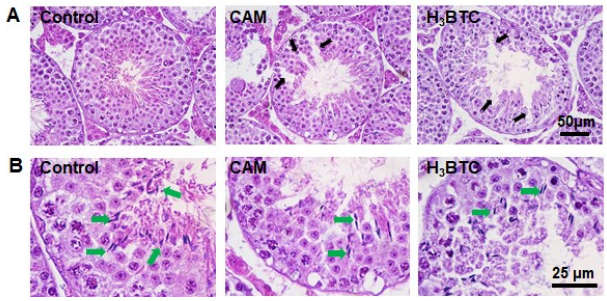


**Figure S9.** The effects of CAM and $H_3BTC$ on seminiferous tubules of male mice. (A) Photographs of seminiferous tubules after H&E staining. Black arrows point to vacuolization. (B) Enlarged H&E photographs of seminiferous tubules showing the spermatids (green arrows) in seminiferous tubules. Arrows point to spermatids.

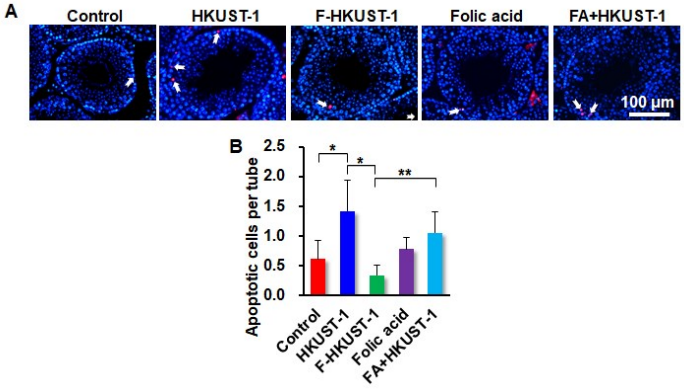


**Figure S10.** Cell apoptosis in seminiferous tubules (20 seminiferous tubules for each mouse). Arrows point to apoptotic cells. (At least 3 mice for each group, $^{*}P < 0.05$, $^{**}P < 0.01$)

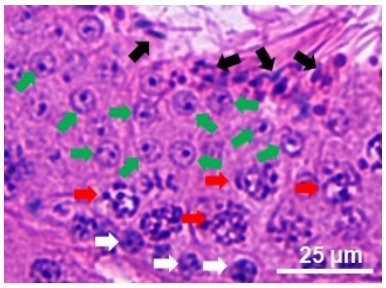


**Figure S11.** Enlarged H&E staining photographs of seminiferous tubules. White arrows point to spermatogonia; Red arrows point to primary spermatocytes; Green arrows point to spermatids; Black arrows point to sperms.

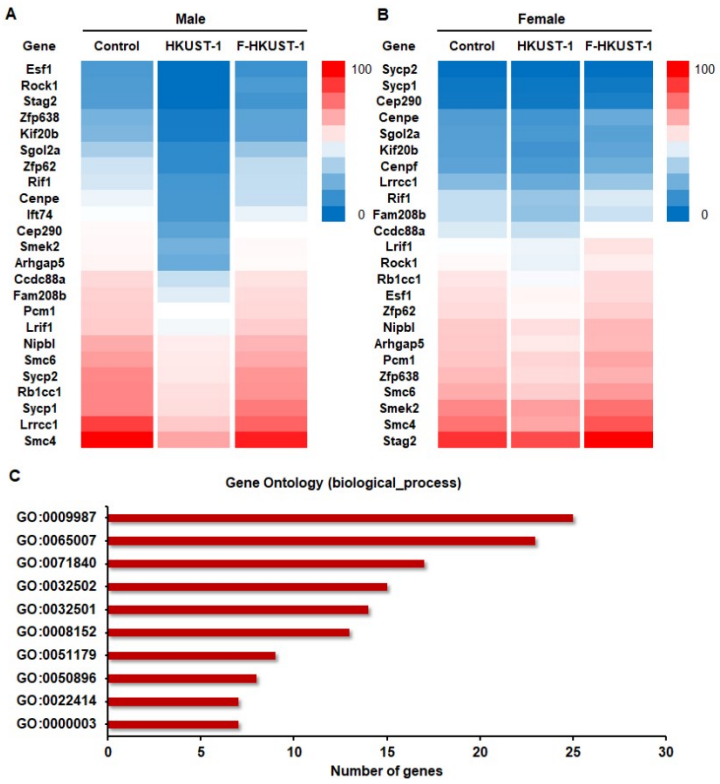


**Figure S12.** The effects of copper MOFs on gene expression of testis and ovary. (A, B) Gene expression in (A) testis and (B) ovary after copper MOF exposures for 30 days. (C) Gene ontology (GO) analysis of gene expression in testis. (3 mice for each group, mean value was used in A and B heat maps). GO terms and corresponding biological processes is available in Table S1.

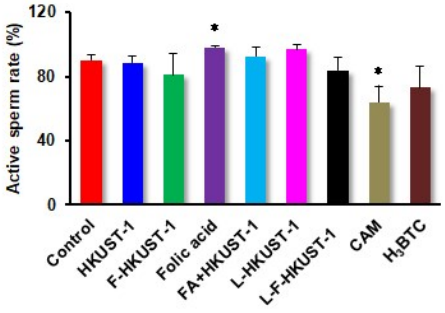


**Figure S13.** Sperm mobility after copper MOF exposures at different copper levels. L-HKUST-1 and L-F-HKUST-1 represent HKUST-1 and F-HKUST-1 at lower dose, respectively. (3 mice for each group, at least 200 sperms for each mouse, $^{*}P < 0.05$ relative to control)

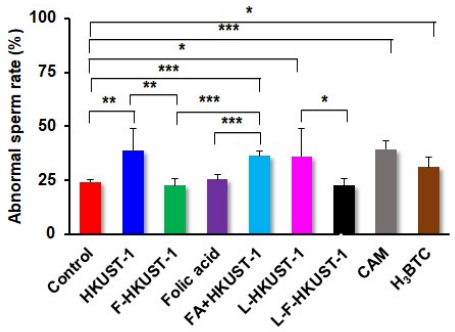


**Figure S14.** Quantitative analyses of abnormal sperms after treatment with CAM, $H_3BTC$, or copper MOFs. L-HKUST-1 and L-F-HKUST-1 represent HKUST-1 and F-HKUST-1 at lower dose, respectively. (200 sperms for each mouse, 6 mice for each group, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)

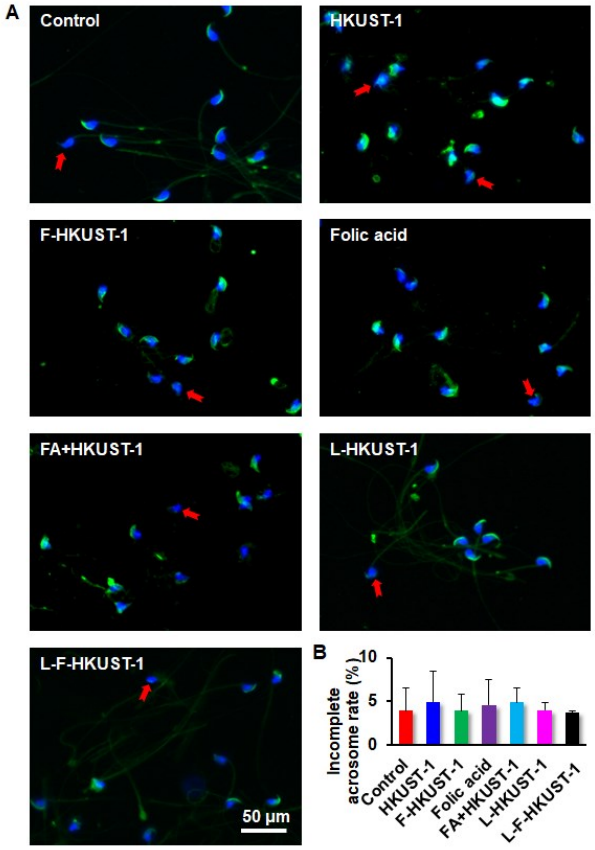


**Figure S15.** (A) Fluorescence photographs of sperm acrosome. Arrows point to sperms without acrosomes. (Sperm nucleus, blue; Sperm acrosome, green). (B) Quantitative analysis of sperms without acrosomes. L-HKUST-1 and L-F-HKUST-1 represent HKUST-1 and F-HKUST-1 at lower dose, respectively. (Around 100 sperms for each mouse, 3 mice for each group)

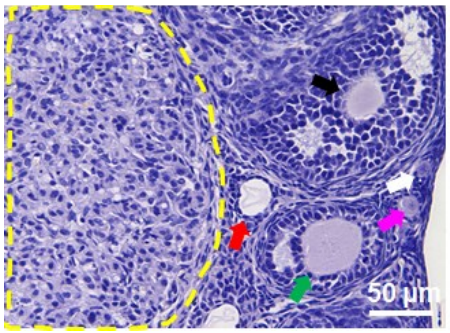


**Figure S16.** Enlarged H&E staining photograph of ovary. White arrow points to primordial follicles; Pink arrow points to primary follicles; Green arrow points to secondary follicles; Red arrow points to mature follicles. Yellow ring encircles corpus luteum.

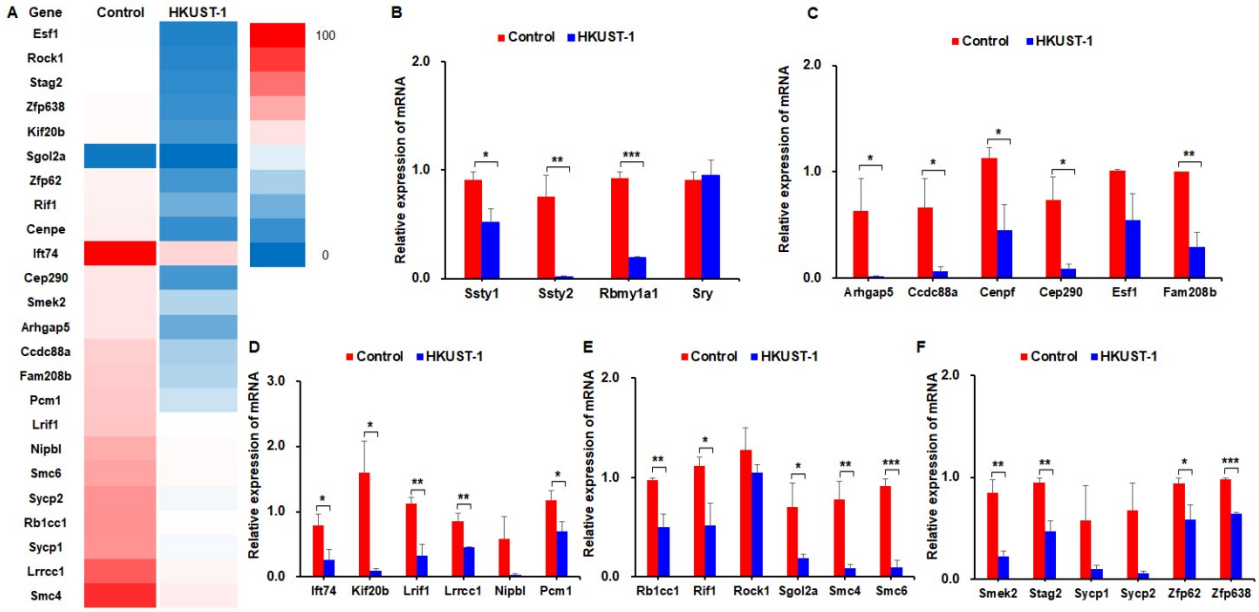


**Figure S17.** The persistence of HKUST-1 effects to testis genes. After treatment for one month, mice were stayed off HKUST-1 for another 46 days, then testis genes were measured using sequencing analysis and Real Time-PCR. (A) Gene expression in testis determined by RNA sequencing. (B-F) Gene expression in testis assessed by Real Time-PCR. (3 mice for each group, mean value was used in heat maps).

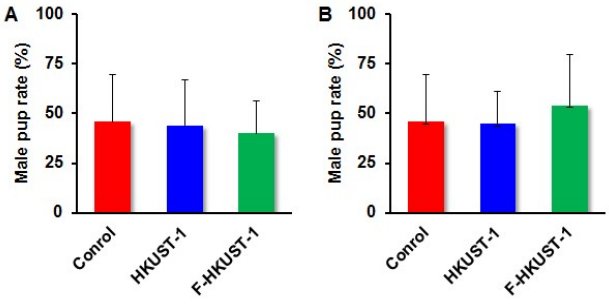


**Figure S18.** The effects of copper MOFs on pup gender. Male pup rate after (A) male mice or (B) female mice were treated with HKUST-1 or F-HKUST-1 for 10 times in one month, respectively. (At least 100 pups for each group)

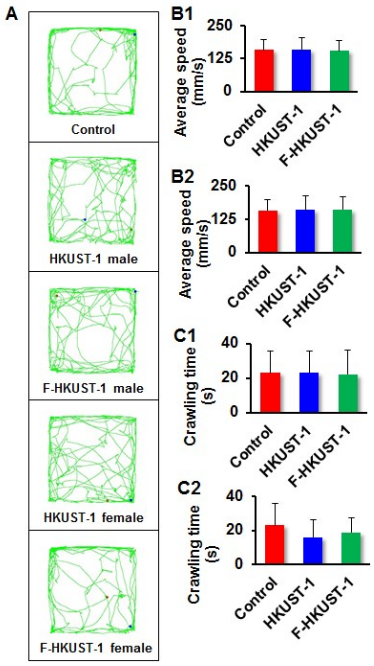


**Figure S19.** The effects of copper MOFs on offspring behaviors. (A) Motion paths of offspring in open-field apparatus. (B) Movement speed of offspring in open-field apparatus for (B1) male or (B2) female parent dosed with copper MOFs. (C) Crawling time of offspring in rotarod test for (C1) male or (C2) female parent treated with copper MOFs. (At least 7 mice for each group)

**Table S1** GO terms and corresponding biological terms.

| GO term | Biological process |
|---|---|
| 0009987 | Cellular process |
| 0065007 | Biological regulation |
| 0071840 | Cellular component organization or biogenesis |
| 0032502 | Developmental process |
| 0032501 | Multicellular organismal process |
| 0008152 | Metabolic process |
| 0051179 | Localization |
| 0050896 | Response to stimulus |
| 0022414 | Reproductive process |
| 0000003 | Reproduction |