

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 31817

Title: A porcine model characterizing various parameters assessing the outcome after acetaminophen intoxication

Dear Professor Ma, dear Reviewers,

Thank you for reviewing the above mentioned manuscript. We found the reviewer's comments very constructive and helpful to improve the manuscript. We tried to address all comments. The changes in the manuscript are highlighted in yellow.

Thank you again for your efforts and help of processing our manuscript.

Sincerely yours,

Christian Thiel and Karolin Thiel

Reviewers Comments:

Major comment:

1. ANOVA test can be used only if more than two groups are compared. There is no "ANOVA t-test" at all. Moreover, ANOVA or t-test can be used only when data exert normal distribution which is not possible to test if there are less than 4(5) samples in the group. Authors should change statistical analysis. They may use one of non-parametric tests or they may compare results after acetaminophen intoxication with the results of the same group at the beginning of the experiment.

We apologize for this mistake. All comparisons were performed by the non-parametric Wilcoxon test.

Mean values were compared by **Wilcoxon test** (JMP® 8.0, SAS Institute, Cary, NC, USA). **Values of the laboratory parameters (Figure 3) were compared to baseline values by the Wilcoxon matched pairs test.**

Minor comments:

1. Plasma/serum activities of ALT and AST and bilirubin level would nicely document the course of ALF.

We appreciate the reviewer's request for additional data. The result section was supplemented with the following data:

The increase of plasma AST (baseline 50 ± 9 U/L vs. ALF 105 ± 28 U/L vs. study end 237 ± 109 U/L) was significant raised ($p < 0.02$) at death compared with baseline values. ALT plasma values did not change substantially during the course of ALF (baseline 33 ± 3 U/L vs. ALF 23 ± 10 U/L vs. study end 26 ± 7 U/L) and total bilirubin plasma levels remained in the physiological range (baseline 0.1 ± 0 mg/dl vs. ALF 0.1 ± 0 mg/dl vs. study end 0.3 ± 0.1 mg/dl).

2. For fixation of histological samples, 4 % formaldehyde or 10 % formalin are used (formalin is 37 % solution of formaldehyde).

We used 4% formaldehyde for fixation of histological samples in our study. We apologize for this mistake and revised the manuscript.

3. In figure 4 legend, I would recommend to add objective magnification.

We appreciate the reviewer's recommendation and added magnification in figure 4 legend.

Bar indicates 200 μ m; objective magnification x 20.

4. Differences in the sensitivity to acetaminophen in this study may be explained by using of female pigs. Sensitivity to toxins may vary across the menstrual cycle. Thus, I would recommend using male pigs in further studies.

The study was performed in eight female German landrace pigs weighing 38 ± 2 kg. Animals of that weight are approximately 100 days old.

(Dewey CE, Straw BE. 2006. Herd examination. In BE Straw, JJ Zimmerman, S D'Alliare, DJ Taylor, eds. Diseases of Swine, 9th ed. Ames, IA: Blackwell Publishing, pp.3-14)

Puberty and estrus in confinement-reared gilts is described to begin at the age of 5 to 6 months.

(Christenson, R.K. and J. J. Ford 1979: Puberty and estrus in confinement-reared gilts. J. Anim. Sci. 49, 743-751)

We discussed the reviewer's comment between the authors and our veterinarian and reached a consensus that differences in the sensitivity to acetaminophen in our study are unlikely to be related to the menstrual cycle.