

Reviewer 1:

1. Please add conclusion section in the text.

Thank you for your comments. The conclusion section has been added at the end of the article (line 505-511).

2. What are the new knowledges from this report?

Thank you very much for your comments. From this report we can know that MCs did exist in the intestine and cause damage to it. Furthermore, the content of MCs in intestine of aquatic organism was higher than that in other organs. However, the content of MCs in intestine of some mammals was less than 0.2% of injected MCs. The discrepancy of MCs in intestine among different species may be explained by the discrepancy of uptake and depuration routes. In addition, the content of MC-LR, MC-RR and MC-YR was also differ in intestine of the same species, it may attribute to the OATP subtype-selective transport of specific MC congeners. It has been elaborated in the first section of the further challenges. Moreover, the mechanisms of MCs on the damage to intestine are not yet clear and further studies are still needed (line 411-421).

3. Please also recommend the readers how to apply this knowledge for routine clinical practice?

Thank you very much for your comments. Microcystins can enter body through oral, inhalation, skin, medical treatment and uptake of aquatic products contaminated by microcystins, etc. Epidemiological surveys showed that microcystins in drinking water sources are one of the major causes of high incidence of primary liver cancer in some areas of southern China. The gastroenteritis of children occurs every year in an area of a specific reservoir water supply in Harare, Zimbabwe. However, children who used other water supplies in the city did not develop gastroenteritis. In 1996, 53 patients died to the dialysate contaminated by MCs. MCs were detected in many drinking water sources especial in Taihu river of Wuxi, China in 2007. Microcystins pose a serious threat to human health. Thus, we advise that in daily life, don't drink water from river, or carry out entertainment projects in water contaminated by water blooms, or eat aquatic products contaminated with microcystins, or use water contaminated with microcystins as medical water in medical treatment, which plays a vital role in preventing the damage of microcystins. This section was added at the last part of the further challenges (line 489-503).

Reviewer 2:

1. The detail mechanism, such as cell signaling or receptors related to mycrocystin.

Thank you very much for your comments. The most important molecular toxic mechanism of MCs in eukaryotes is it can strongly and specifically inhibit the activity of serine and threonine proteins phosphatase 1 and 2A (PP1 and PP2A) which involves in many important intracellular processes such as cell growth, differentiation, protein synthesis, cell signaling, etc. Studies have confirmed that there is an irreversible covalent bond between MCs and PP1/PP2A. The toxic mechanisms have been reported in the small intestine are related to oxidative stress and the expression of apoptosis-related proteins after exposed to MC-LR. Therefore, further studies are needed to explore the specific cell signaling or receptors in MC-LR-induced intestinal damage. This section was added at the second section of the further challenges; other mechanisms that

could damage the intestines may exist (line 451-460).

2. The interaction of mycrocystin and gut microbiota, what is the present status.

Thank you very much for your comments. In human gastrointestinal ecosystem, there are enormous and complicated microbes named as gut microbiota which is combined in a certain proportion for each bacterium. They constrain each other and depend on one another for existence to form an ecological balance in quality and quantity. It will cause many diseases once this balance broken. Studies found that MC-LR can increase the microbial species richness as well as the microbial diversity in the caecum and colon with no effect in the jejunum-ileum, among which, the increase of *Barnesiella* in *Porphyromonadaceae* was most remarkable. Therefore, the toxicological effects of MC-LR varied between the jejunum-ileum and the other two gut regions. However, there are few studies on the effects of MC-LR on gut microbial. The gut microbial has a significant impact on human health as the first defense line in the intestine. Therefore, the effect of MC-LR on the intestinal flora needs to be further studied. This section was added at the last part of pathological effect of MCs in the intestines (line 381-393).

3. The conclusion may be revised more concise.

Thank you very much for your comments. The concise conclusion has been added at the last of the article (line 505-511).