Point by point responses to the reviewers

Reviewer #1:

Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Specific Comments to Authors: General comments

1. **How safe are the high doses -liver, renal toxicological studies ?It appears it induces fatty liver -can you provide liver TG to confirm this？**

We thank the reviewer for this comment. BDE-209 shows very low toxicity, but higher doses of BDE-209 can accumulate in organisms, producing toxic effects. In this study, the dose of each exposure group was determined by referring to related research and pre-experimental findings.

This study detected levels of blood lipids such as TG in serum. Liver tissues were examined for their mRNA and protein levels of leptin, adiponectin, and PPARγ. The contents of TG in liver tissue was not determined. However, we observed pathological changes of liver tissue. These results showed that BDE-209 exposure created a disordered structure of liver tissue. Liver sinusoids and hepatocytes were irregular, accompanied by local inflammatory cell infiltration, indicating that BDE-209 caused liver tissue inflammation that could further progress to fatty liver.

2. How do you explain the decrease in plasma insulin-beta cell toxicity -impaired insulin secretion This ？

We thank the reviewer for this comment. Possible reasons for impaired insulin secretion include: 1) BDE-209 may induce inflammation or oxidative stress that damages pancreatic tissue, and thus affects the synthesis and secretion of insulin by pancreatic β cells, reducing insulin levels; 2) BDE-209 increases leptin expression, and high levels of leptin inhibit the synthesis of β cells in the pancreas, resulting in decreased insulin secretion.

3. Explain why HOMA was not increased with the higher doses PPARS-gamma agonist like

pioglitazone increase adiponectin and improve insulin sensitivity but you show the reverse of increase PPARS-g with decrease adiponectin

We thank the reviewer for this comment. BDE-209 can cause abnormal differentiation of mouse adipocytes, and adiponectin is an adipocytokine secreted by adipocytes. Abnormal adipocyte differentiation can lead to decreased adiponectin secretion. PBDEs may be ligands of PPARγ. After activating the PPARγ receptor, PPARγ expression increases. The mechanism by which the PPARγ activator BDE-209 affects adiponectin secretion is as follows: after PPARγ is activated by the ligand BDE-209, it binds to retinol X receptor (RXR) to form a heterodimer. By binding to the PPARγ response element (PPRE) on the specific DNA, the downstream genes of PPARγ cannot function as normal. Ultimately, this causes reduced adiponectin levels. Adiponectin is an effective insulin sensitizer in the body. Decreased adiponectin content leads to decreased insulin sensitivity.

4. There is a paradox between adiponectin protein and mRNA especially in liver please discuss

We thank the reviewer for this comment. There is a contradiction between the downregulation of adiponectin protein in liver cells and the upregulation of adiponectin mRNA. Potential reasons are as follows: 1) although there is a considerable amount of mRNA during the translation, post-translational processing, modification, and degradation steps for the adiponectin gene product, the protein level is low due to low translation efficiency; 2) because the detection times are different, the protein levels are still increasing when the mRNA reaches its peak.

5. Please use Adp or Adipo to abbreviate adiponectin -ADP is a unique biochemical molecule derived from ATP

We thank the reviewer for this comment and have made the requested edits.