

Peer Review

Review of: "Thermal and Packaging-Related Nanoparticles in Food: Formation Pathways, Migration Mechanisms, and Toxicological Considerations"

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Major Revision Comments

1. The introduction is comprehensive but could better define the scope of the review and its unique contribution relative to existing reviews on food-related nanoparticles. Clearly state whether the review aims to provide a mechanistic understanding, summarize toxicological data, or highlight regulatory implications.
2. The manuscript primarily summarizes existing studies but does not critically compare results or discuss inconsistencies between studies (e.g., why pork-derived NPs cross the blood-brain barrier while chicken-derived NPs do not). A deeper critical evaluation would significantly improve the impact of the review.
3. The section on CNP formation mechanisms could benefit from schematic diagrams or flowcharts to visualize the Maillard reaction, caramelization, and ROS involvement leading to CNP formation. This would improve reader comprehension and highlight knowledge gaps.
4. The review lists biodistribution and cytotoxicity data from multiple studies but does not adequately integrate them into a coherent picture of risk. Consider including a table summarizing doses, models used, endpoints measured, and observed effects to allow for cross-study comparisons.
5. Some toxicological studies cited use very high NP doses that may not be environmentally or nutritionally relevant. The review should clearly differentiate between realistic human exposure levels and experimental doses used in animal studies.
6. The regulatory perspectives section mentions EFSA and FDA guidelines but could be expanded to include international perspectives (e.g., Codex Alimentarius, ISO standards). A discussion of current gaps

in risk assessment methodology, such as the lack of chronic exposure data, would be valuable.

7. The discussion of analytical methods should be expanded to highlight the lack of validated, inter-laboratory standardized protocols. Recommend potential harmonization efforts (e.g., ISO/ASTM standards) to improve comparability across studies.

8. Several sections are lengthy and could be streamlined for readability. For example, the description of individual studies (meat, pizza, squid, lamb) could be condensed and summarized in a comparative table, with more emphasis placed on the implications of their findings.

9. Add more visual elements (schematics, comparative tables, risk assessment flowcharts). Figure 1 is helpful, but additional visual summaries could enhance accessibility for readers.

10. The "Research Needs and Future Directions" section should be more actionable. Specify priority areas (e.g., chronic low-dose exposure studies, human biomonitoring, interaction with the gut microbiome) and suggest interdisciplinary approaches to address them.

Declarations

Potential competing interests: No potential competing interests to declare.