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Metformin in a warming world: The hidden danger to freshwater ecosystems

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Abstract

Background: Metformin (MET), a widely prescribed drug for type-II diabetes mellitus, is increasingly detected in aquatic environments due to its high consumption and inefficient removal during wastewater treatment [1]**.** Concomitantly, freshwater ecosystems are experiencing intensifying thermal stress driven by climate change, which may modulate contaminant toxicity and challenge ecological risk predictions [2]**. Objective:** This study evaluated how thermal stress modulates the long-term ecotoxicological effects of MET in *Daphnia magna,* combining life-history traits with sub-individual physiological responses. **Methods:** Standard *D. magna* reproduction tests were conducted following OECD 211 guidelines [3], exposing organisms to 0-100 µg MET/L for 21 days at two temperatures: 20 °C (standard conditions) and 24 °C (warming scenario reflecting the + 4 °C increase projected by the IPCC until 2100). To evaluate potential impairments in feeding behavior after chronic exposure, post-exposure feeding inhibition assays [4] were performed after a 24h depuration period in clean medium, followed by a 4h feeding phase. Biomarkers related to oxidative stress, detoxification and neurotoxicity were quantified. **Results:** Temperature strongly influenced the reproductive responses of *D. magna*. At 20 °C, MET exposure induced concentration-dependent responses in key reproductive parameters, including fertility, reproductive output, and first brood fecundity. Under the warming scenario (24 ºC), *D. magna* exhibited an overall enhancement of reproductive performance, with earlier maturation, increased offspring production and fecundity, higher reproductive output, and greater population growth rates. While MET exposure did not affect *D. manga* feeding behavior at 20 ºC, a significant decline in feeding rate was observed at all MET concentrations at 24 ºC. Preliminary biomarker analysis further suggests that MET-induced physiological responses are temperature-dependent. **Conclusions:** Thermal stress appears to reshape the ecotoxicological responses to MET in *D. magna*, influencing both organismal performance and physiological status. By integrating life-history traits with mechanistic biomarkers, this study provides a multilevel understanding of MET effects under climate-driven warming. These findings highlight the importance of incorporating multi-stressor and multi-level approaches into future ecological risk assessment frameworks.

Keywords: pharmaceuticals; climate change; model organisms

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