

Maternal Exposure to Diisononyl Cyclohexane-1,2-Dicarboxylate as a Risk Factor for Metabolic Dysfunction-Associated Steatotic Liver Disease in Mouse Offspring

Vasilije Živaljević, Milivoje Konstantinović, Sanja Kovačević, Ana Djordjevic, Danijela Vojnović Milutinović, Goran Đmura and Nataša Veličković

Department of Biochemistry, Institute for Biological Research “Siniša Stanković” - National Institute of Republic of Serbia, University of Belgrade, Belgrade, Serbia



INTRODUCTION

Diisononyl cyclohexane-1,2-dicarboxylate (DINCH) is a non-phthalate plasticizer increasingly used as a replacement for traditional phthalates in medical devices, food-contact materials, and consumer products. Despite its widespread use, the long-term metabolic consequences of developmental DINCH exposure remain poorly understood.

Increasing evidence implicates **endocrine-disrupting chemicals (EDCs)** in the development of **metabolic dysfunction-associated steatotic liver disease (MASLD)**. However, the molecular mechanisms linking developmental DINCH exposure to altered liver metabolism remain largely unknown, particularly the potential involvement of hepatic glucocorticoid signaling.

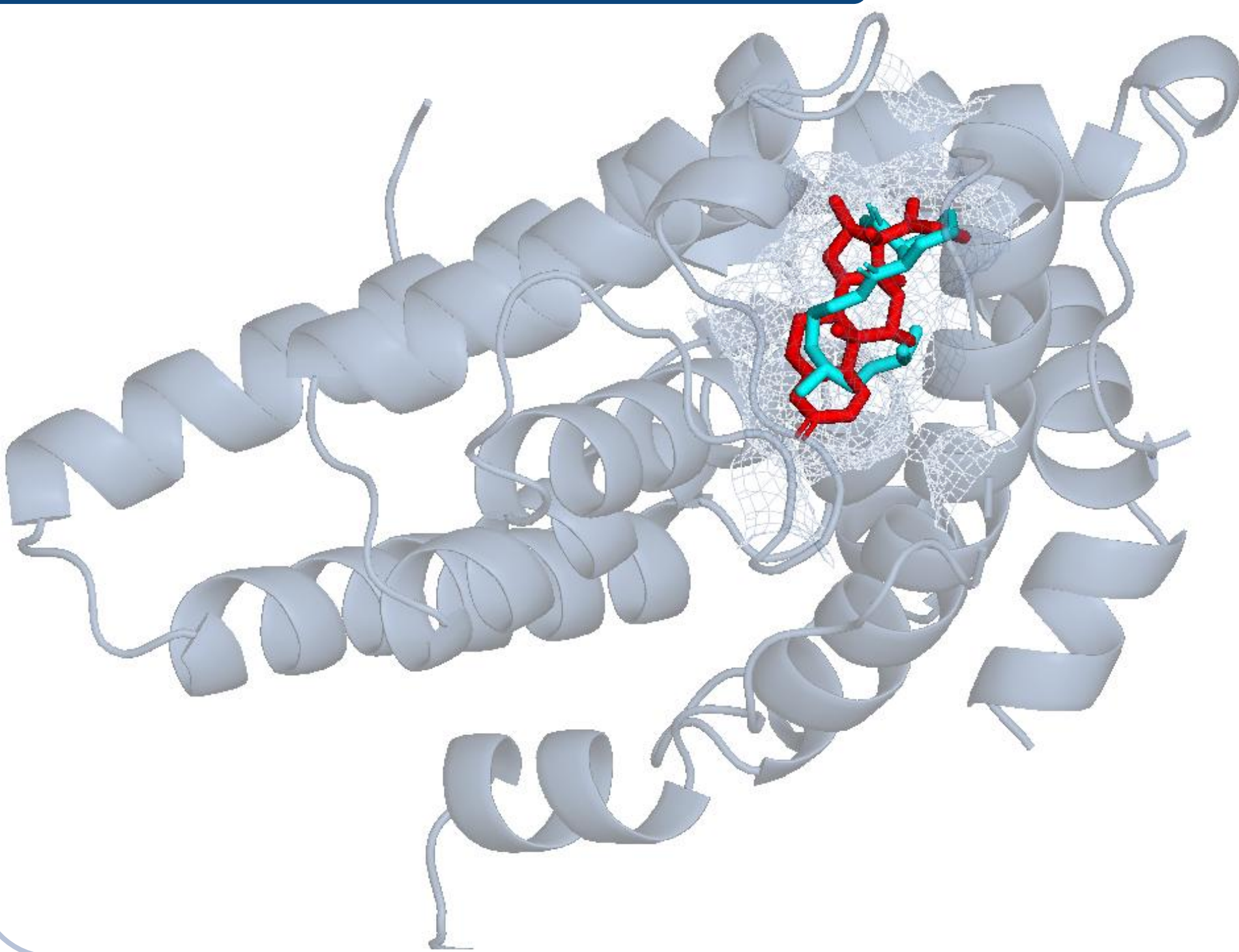
This ongoing study investigates whether maternal DINCH exposure increases susceptibility to MASLD in offspring and whether hepatic glucocorticoid signaling contributes to these effects in a sex-dependent manner.

WHY GR?

Glucocorticoid receptor (GR) signaling is an important regulator of hepatic glucose and lipid metabolism, and its dysregulation has been implicated in metabolic dysfunction and **MASLD**. Endocrine-disrupting chemicals may interfere with nuclear receptor signaling.

Could DINCH interfere with hepatic GR signaling during early life exposure?

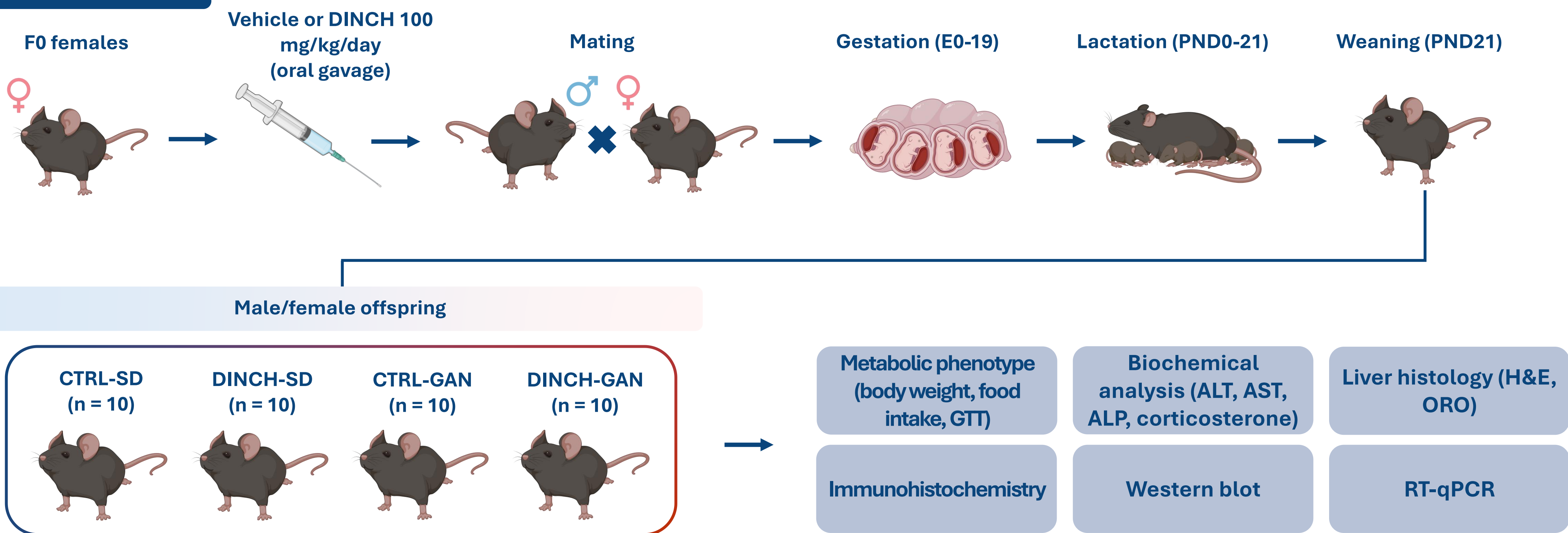
PRELIMINARY *IN SILICO* RESULTS



BINDING AFFINITY	
DEXAMETHASONE	-12.62 kcal/mol
OH-MINCH	-7.83 kcal/mol
DINCH	-6.87 kcal/mol

OH-MINCH localizes within the canonical **GR ligand-binding pocket** and partially overlaps with dexamethasone, suggesting a potential interaction with GR.

EXPERIMENTAL DESIGN



EXPECTED OUTCOMES

This study is expected to clarify whether developmental DINCH exposure predisposes offspring to MASLD and to provide insight into the molecular mechanisms underlying its metabolic effects. Particular emphasis will be placed on hepatic glucocorticoid signaling as a potential pathway linking early-life DINCH exposure to altered liver metabolism and increased disease susceptibility. By evaluating both male and female offspring, the study will also determine whether these responses are sex-dependent. Overall, the findings are expected to improve our understanding of the long-term metabolic consequences of developmental DINCH exposure and contribute to the toxicological evaluation of this increasingly used plasticizer.

This project has received funding from the Horizon Europe research and innovation program of the European Union under Grant Agreement 101136259.



Funded by
the European Union