# Novel Insights of $Pb^{2+}$ Exposure, and Dietary Carbohydrate Stress in the causation of pathologies allied with Type 2 Diabetes Mellitus

**A THESIS**

**Submitted for the Degree of**

**DOCTOR OF PHILOSOPHY**

**in Biological Science**


**Submitted By,**

**P. Vineeth. Daniel (D16075)**

**Under the supervision of**

**Dr. Prosenjit Mondal (Assoc. Prof)**




**School of Basic Sciences**

**Indian Institute of Technology, Mandi**

**Mandi (175005), Himachal Pradesh, India**

# DECLARATION BY THE RESEARCH SCHOLAR

I hereby declare that the entire work embodied in this thesis is the result of investigations carried out by me in the **School of Basic Sciences**, Indian Institute of Technology Mandi, under the supervision of **Dr. Prosenjit Mondal**, and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work utilizes an effort of other investigators.

Date: 22nd June 2021
Place: Mandi, H.P.

**Mr. P. Vineeth. Daniel**
Enrolment No: D16075
SBS, IIT Mandi

# DECLARATION BY THE ADVISOR

I hereby certify that the entire work in this Thesis has been carried out by **Mr. P. Vineeth Daniel**, under my supervision in the **School of Basic Sciences**, Indian Institute of Technology Mandi, and that no part of it has been submitted elsewhere for any Degree or Diploma.

Date: 22nd June 2021
Place: Mandi, H.P.

**Dr. Prosenjit Mondal**
Associate Professor
SBS, IIT Mandi

*Dedicated to my Parents, Teachers, Friends*

*and especially to the Animals sacrificed for this study*

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Date: 22nd June 2021 **Mr. P. Vineeth. Daniel**

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# ABSTRACT

Metabolic disease is a global concern, and the rate of its escalation is petrifying. Although multiple pathophysiologies are regarded under the heading of metabolic diseases, Type 2 Diabetes Mellitus (T2DM) ranks to be one of the most threatening. Pouya Saeedi et al. (2019) accounts prevalence of T2DM to rise from 520million cases (in 2030) to 630million cases by 2045. Although the onset and progression of T2DM show a multi-faceted regulation, the conventional causative factors fail to account for this mounting threat. Thus, it stands imperative to look for newer unexplored, unconventional causative factors that could directly or indirectly influence the onset and progression of T2DM.

Human activities-induced release of xenobiotics across the environment intimates heavy metal contamination as the upcoming threat over the orthodox causes. Reports highlight Lead ($Pb^{2+}$) as the looming endocrine & metabolic disruptor but does not provide any additional comprehensions about its mode of action. At this juncture, this thesis investigates and presents mechanistic understandings of $Pb^{2+}$ induced metabolic abnormalities. This study presents a comprehensive idea regarding $Pb^{2+}$ induced pancreatic β-cell dysfunction and T2DM occurrence *in vivo*. This study also explains $Pb^{2+}$ induced hepato-toxicity and fatty liver pathologies. Motivated with the non-nutrient ($Pb^{2+}$) induced pathophysiology of Non-Alcoholic Fatty Liver Disease (NAFLD), this study unveils a definite mechanism of conventional high carbohydrate diet-induced NAFLD via ChREBP. Taken together, this thesis dually targets T2DM by presenting a new credible "non-nutrient" culprit and by discovering a novel mechanistic insight of hepatic dyslipidemia, which if targeted can indirectly encourage a reduction in hepatic pathologies linked to T2DM aggravation.