

# NSF FINAL REPORT

## Section 1

### Information regarding project/project personal:

- i) Grant Number: RG/2008/BS/01
- ii) Title of the Project : **Equilibrium studies on toxic metal ion-mixed ligand systems under physiological conditions.**
- iii) Principal Investigator : Dr. Champika V. Hettiarachchi, Department of Chemistry, University of Peradeniya
- iv) Co-Investigator : Prof. O.A. Ileperuma, Department of Chemistry, University of Peradeniya.
- v) Institute where research was being carried out : Department of Chemistry, Faculty of Science, University of Peradeniya.
- vi) Date of award : 01<sup>st</sup> of September, 2008.
- vii) Date of completion of project : 31<sup>st</sup> of August, 2011.
- viii) Total allocation of funds : Rs. 1,490,000.00
- ix) Total spent : Rs. 1,383,831.41
- x) Number of research students employed: 01
- xi) Postgraduate degree completed with dates : none first draft of the thesis will be submitted in the first week of March, 2012
- xii) Number of technical assistants and/labours employed and period of service : none
- xiii) Publications/ communications arising from the project during the reporting period : 4

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## Section 2

### Executive summary of the project:

The study of toxic metal complexes has become a worldwide interest related to various aspects such as, investigation of effective metal chelators for chelation therapy and removal of toxic metals from water reservoirs, etc. However, the research done on interactions between toxic metals and mixed ligand systems is very rare especially with ligands entering to our body more frequently. The main focus of the study was the investigation of mixed ligand complexes of toxic metals to find out their bioavailability and to discover less harmful ligand combinations for chelation therapy.

Thus, this project explored the equilibrium study on  $Pb^{2+}$ ,  $Cd^{2+}$ ,  $Al^{3+}$  and  $Cu^{2+}$  toxic ions and ascorbic acid, paracetamol, salicylic acid, citric acid, uracil, aspirin, vitamin B<sub>1</sub>, vitamin B<sub>3</sub>, caffeine and Na<sub>2</sub>EDTA using pH titrations and UV-Visible spectroscopy under the physiological conditions of  $37.0 \pm 0.2$  °C and 0.15 M ionic strength. The analysis revealed that all four metal ions have significant interactions with each ligand alone and with ligand mixtures. Though, Na<sub>2</sub>EDTA was the strongest ligand bound to four metal ions in binary complex formation, there were several mixed complexes for each metal, which were more stable having several hundred times larger stability constants than M-EDTA complexes. Specially,  $Pb(Na_2EDTA)(VitaminB_1)$ ,  $Pb(Na_2EDTA)(Ascorbic\ acid)$  and  $Pb(Na_2EDTA)(Citric\ acid)$  had remarkably high stability in mixed complexation with four metals. As most mixed ligand complexes had stability constants greater than 6, they were all good for chelation therapy with fewer side effects, especially with non EDTA ligand combinations. Further work revealed

that, the bioavailability of paracetamol, Ascorbic acid, Vitamin B<sub>1</sub> will be lower for a metal intoxicated person.

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### Section 3

#### Report in detail:

#### Introduction /background:

More than half of the elements found in nature are metals. Out of them, some of the heavy metals like lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), chromium (Cr) and antimony (Sb) etc. are toxic to the biological systems as they tend to make undesirable effects in the biological systems if they are present in significant amounts. Therefore, they are known as toxic metals.

Today entire earth; soil, Water and air consist of at least several toxic metal ions in considerable concentrations due to various human activities. Hence, many food items and beverages contain toxic metal ions and ultimately enter into the human body<sup>1-3</sup>. Once they are adsorbed in both bronchial tubes and gastrointestinal tract, they will be transported by the blood stream into the cellular fluids, where toxic metals exert their toxic effect<sup>1</sup>. Toxic metals can make several imperfections in many systems in the human body including central nerves system, the cardiovascular system, respiratory system and the hematopoietic systems<sup>1&4</sup>, due to very high affinity for certain active groups on plasma proteins; especially macromolecular fractions of the protein<sup>5,6,7,8</sup>.

Among all the toxic metals, lead is the one distributed largely. Lead can be absorbed into the biological systems either as an organic molecule or as an inorganic one. Hence, lead is absorbed in both water soluble part and water insoluble lipid part of biological systems. Because of that, lead can be found in blood as well as in skeleton<sup>4</sup>. However frequent exposure to lead for a long time will result in diseases like impaired kidney functions, multiple sclerosis, anaemia, neurological diseases and encephalitis<sup>1,7,8</sup>. More common issue found in developing countries like Sri Lanka is that the toxicity arises due to the use of aluminium and metal coated utensils, paints and pigments containing heavy metals. Cadmium can be found very often in commercial zinc and can be entered to the living systems by the use of galvanized material. On the other hand, cadmium poisoning can frequently be seen due to consumption of vegetable and fruits contaminated by cadmium because of the agricultural use of cadmium containing fertilizers and soil contaminated by sewage sludge. Each cigarette contains significantly higher amount of cadmium and more than half of that may enter into the lungs during smoking. After a period of time, such an individual can suffer from chronic renal failure leading to renal diseases<sup>9</sup> and a painful disease due to the erratic bone metabolism known as "itai-itai byo"<sup>1</sup>. Being the most abundant element in the earth's crust, aluminium can be found alone and in many organic and inorganic molecules. There are several roots like, from the environment, from foods and beverages, from health care agents, from various administrations as an antacid, anti-diarrheal or as anti-phosphate absorbers through which aluminium can enter into humans. There is a risk of aluminium toxicity as a result of using aluminium utensils in cooking<sup>10</sup>. Dialysis encephalopathy<sup>11</sup>, fractures and high levels of bone aluminum<sup>11,12</sup> and Alzheimer's disease<sup>12</sup> are some of those commonly identified diseases due to excessive intake of aluminium. By the definition, copper is an essential element for the activity of different enzymes such as tyrosinase, amine oxidase, cytochrome oxidase, ceruloplasmin and ascorbic acid oxidase etc. Hence, without copper some essential biological functions will not take place. Diseases like Anemia, kinky-hair syndrome can be seen due to copper deficiency. However, if uptake level of copper is too high, then