PREFACE

As a consequence of rapid industrialization, modernization and change in life style, a large number of pollutants having mutagenic and carcinogenic potential are being continually introduced in the environment. The bio-magnification of such toxic substances takes place in the ecosystem leading ultimately to rather hazardous situations. Human beings in their living and working environments ingest, inhale and absorb many chemicals that can impose stress and trigger tissue damage by numerous bio-chemical and cellular mechanisms. Some such chemicals viz., chromium, arsenic, aluminium, fluoride, mercury, lead, nickel etc. if taken beyond permissible limits are proven toxicants.

The main objectives in undertaking this work were to study:

1. The effects of aluminium and fluoride alone and in combination *in vivo* on some soft tissues of female mice and *in vitro* studies on peripheral blood lymphocyte cultures for assessment of genotoxicity.

2. To investigate the possible therapeutic effects of calcium, vitamins C and E alone and in combination *in vivo* and the protective effect of vitamin C against aluminium and fluoride toxicity *in vitro*.

Aluminium (Al) is a ubiquitous metal which is potentially toxic to man. The toxicity of Al in patients with chronic renal failure particularly on the different dialysis treatment have been well documented. Aluminium has been implicated as an aetiological factor in several diseases such as Alzheimer’s disease and Parkinson’s dementia. It is necessary to assess the
risk of Al exposure because it is one of the most abundant elements of the earth’s crust and its compounds are widely used in medicine and as cookware. Present knowledge on toxic effects of Al is rather sparse, and work should be carried out in this direction.

Fluoride is a two-edged sword for human health. On one hand fluoridation of drinking water seems to be effective for the treatment of dental caries and osteoporosis, while on the other hand, excess fluoride intake leads to its toxic effects and causes fluorosis. Fluoride toxicity is not only confined to the skeletal tissues but its harmful effects on central nervous system, gastrointestinal tract, liver, kidney, cardiovascular system, respiratory system, reproductive system and muscle have also been known. In a country like India, fluoride levels in water range from 1.0 – 48 mg / L. Fluoride alters the permeability of membranes and has an adverse effect on many enzymes even at low concentrations. As there is paucity of data regarding fluoride toxicity on soft tissues, studies in this direction are necessary.

Fluoride and aluminium are found together in nature as an ore – Cryolite (Na₃AlF₆). Combined effects of F and Al in biological systems are very contradictory and not well understood. Some studies have shown that fluoride promotes absorption of aluminium in the gastrointestinal tract, while others indicate that aluminium protects from fluoride toxicosis by forming stable complex thereby increasing fecal excretion. Hence, for further understanding of fluoride and aluminium combined toxicosis, the present work was undertaken.
Some therapeutic agents like vitamin C, D, E calcium, protein rich diets, amino acids like glycine and glutamine are known to ameliorate toxicity induced by different chemicals. It is of prime importance to study their therapeutic property against toxicity of fluoride and aluminium administered alone or in combination.

Aluminium and fluoride alone and in combination caused alteration in the body and organ weights and changes in several enzyme activities. NaF, AlCl₃ and NaF+AlCl₃ treatments resulted in disturbances in protein, carbohydrate, lipid, nucleic acid and oxidative metabolisms.

The treatments caused hypercholesterolemic effect and increased levels of cholesterol in ovary with simultaneous decline in the activities of 3β and 17β hydroxysteroid dehydrogenases, suggesting altered steroidogenesis.

The activities of some specific enzymes of liver, muscle and brain declined which may affect carbohydrate and oxidative metabolism in these organs.

The DNA and RNA levels of liver, gastrocnemius muscle, cerebral hemispheres of the brain and ovary showed alterations after the treatments suggesting disturbances in nucleic acid metabolism.

Serum protein, cholesterol, SGPT and SGOT levels increased significantly indicating changes in protein and lipid metabolisms and liver function.
NaF, AlCl₃ and NaF+AlCl₃ treatments induced formation of free radicals in liver, gastrocnemius muscle, cerebral hemispheres of brain and ovary. Lipid peroxides increased while glutathione levels decreased and activities of superoxide dismutase (SOD), catalase, glutathione peroxidase, declined in these tissues. These changes cumulatively rendered the tissues susceptible to injury. The total and reduced ascorbic acid levels decreased with increased accumulation of dehydro-ascorbic acid suggesting stress imposed by fluoride and aluminium in these tissues.

The genotoxic studies on NaF, AlCl₃ alone and in combination revealed significant increase in the frequency of sister chromatid exchanges, chromosomal aberrations and aneuploidy. There was also a significant increase in the number of micronuclei induced by cytochalasin-B indicating possible increase in non-disjunction by fluoride and/or aluminium. The cell cycle was impaired by fluoride or aluminium and more so by their combined treatments. Changes in the frequency of telomeric and acrocentric association might indicate that these chemicals may potentially cause precocious aging and accelerating tumourigenesis.

The above results suggest that fluoride and aluminium alone and in combination affected reproductive and some non-reproductive tissues of female mice and they were capable of causing genotoxic effects. Of all the treatments viz., NaF, AlCl₃ and NaF+AlCl₃, the co-treatment of fluoride and aluminium was most toxic.
The treatment of calcium, vitamin C and vitamin E alone caused a significant recovery in all the parameters studied in all the organs. Maximum recovery was obtained by combined administration of these antidotes.

The above data therefore suggest that fluoride and aluminium induced toxicity is transient and reversible by some therapeutic agents. The study may also help in understanding the mechanism of action of fluoride and aluminium induced toxicity and its amelioration and is an important contribution to our knowledge in the field.

The thesis consists of:

CHAPTER I GENERAL INTRODUCTION AND REVIEW OF LITERATURE
CHAPTER II MATERIALS AND METHODS
CHAPTER III RESULTS - IN VIVO AND IN VITRO STUDY
CHAPTER IV DISCUSSION - IN VIVO AND IN VITRO STUDY
CHAPTER V SUMMARY AND CONCLUSIONS

In the end, a BIBLIOGRAPHY in alphabetical and chronological order is given.