| 京都大学 | 博士（都市環境工学） | 氏名 | TAN SHIH WEI |
|---|---|---|---|
| 論文題目 | Toxicity Evaluation of Gallium- and Indium-Related Chemicals by Using Freshwater Amphipod (*Hyalella azteca*) and Human Cultured Cells<br>（淡水性ヨコエビおよびヒト培養細胞を用いたガリウムとインジウム化合物の毒性評価） | | |

（論文内容の要旨）

The rapid development of emerging technologies has been relevant to technology-critical elements of concern. Among those elements, gallium (Ga) and indium (*In*) are important raw materials in semiconductors and optoelectronic industries, and the enhanced production of the two metals has increased the distribution of Ga and In in the environment through the industrial manufacturing processes, especially in discharging of sewage in water bodies. Also, the workers engaged in the indium tin oxide (ITO) production line and e-waste recycling progresses are potentially exposed to Ga- and In-containing dusts. Occupational inhalation exposure to *In*-containing dusts (*e.g.*, ITO, $In_2O_3$) has been demonstrated to cause indium lung disease. Although there has been progress in investigating and understanding the interaction of Ga and In with biological systems, much remains to be learned about their interaction with other Fe-dependent and Fe-independent processes.

In Chapter 1, chemical transformation, bioavailability, short-term and long-term toxic effects of ion species and insoluble hydroxide/oxide chemicals of Ga and In in the aquatic environment were introduced. In Chapter 2, we focused on exploring the interaction of Ga and In with biological systems, which was either Fe-dependent or Fe-independent processes. Moreover, the potential biological factors and/or modes of action related to chronic human health such as indium lung disease, senescence, and carcinogenicity were also investigated.

The research purpose of Chapter 1 aims at investigating the effects of aqueous chemical transformation on the bioavailability, toxicity (acute and chronic) and potential impacts of Ga- and In-related chemicals, including In(III), citrate-In(III), Ga(III), citrate-Ga(III), $In(OH)_{3(s)}$, $In_2O_{3(s)}$ and $Ga_2O_{3(s)}$, by using freshwater amphipod (*Hyalella azteca*) *in vivo* bioassays. The present study provides new insight into the aquatic toxicity of Ga- and In-related chemicals that have not previously been evaluated in epibenthic freshwater amphipod. Our results proposed that the lower levels of In(III) and Ga(III) exposure, the higher toxic effects would be induced due to hydrolysis in higher concentrations. Furthermore, the use of metal chelator such as citrate could affect hydrolysis of both Ga(III) and In(III), thereby increasing their bioavailability and toxicity to *H. azteca*. We also investigated that the hydrolysis products of In(III), Ga- and In-based hydroxide/oxide chemicals may have lethal and sublethal effects, which appeared to be affected by environmental factors (*e.g.*, water temperature) relating to locomotor and feeding behaviors.

| 京都大学 | 博士（都市環境工学） | 氏名 | TAN SHIH WEI |
|---|---|---|---|

Since the workers engaged in In and Ga processing are potentially exposed to In- and Ga-containing aerosols through inhalation, which have known to increase serum indium levels and the risk of indium lung disease (interstitial pneumonia and pulmonary fibrosis) and lung cancer. The latency period (month to years) of indium lung disease is relatively shorter than other occupational lung disease such as silicosis and asbestosis. So far, the entire pathogenesis of indium lung disease and factors affecting the latency period in this disease remain elusive, the available evidence indicates that the pathogenesis is closely associated with dissolved and accumulated indium in the body. The main modes of toxic action of Ga and In to humans could be categorized into two types, Fe-dependent and Fe-independent pathways. However, there is still a large gap in knowledge about the relationship between the exposure of Ga- and In-related chemicals, pathogenic mechanisms, and chronic health effects. Therefore, the research purpose of Chapter 2 aims to investigate the biological factors that potentially associated with chronic health impacts of occupational exposure to Ga- and In-related chemicals and the progression of indium lung disease.

Chapter 2 provides new insight into the potential role of In-induced cellular senescence in the pathological progression of indium lung disease. In recent years, the aging-related lung diseases have been identified to be associated with alterations in lung function, increased susceptibility to acute and chronic lung diseases, such as obstructive and fibrotic lung disease. The hallmarks of cellular aging include genome-based failures (genomic instability, telomere attrition, epigenetic alterations), signaling dysfunction (deregulated nutrient sensing, altered intercellular communication), organelle compromise (mitochondrial dysfunction, loss of proteostasis), and cell phynotypic changes (stem cell exhaustion, cellular senescence). Our results demonstrated that In(III) and Ga(III) could induce mitochondrial abnormalities and cellular senescence based on Fe deficiency stress. Other toxic outcomes regarding Fe-independent pathways also indicated the two metals may disturb proteasome homeostasis and cause DNA damage. These hallmarks of cellular aging appeared to accelerate cellular senescence processes, and eventually affect the rate of pathological progression of indium lung disease.