中文摘要

本論文提出以生理學及生物能量學為基礎之研究架構探討砷在吳郭魚(*Oreochromis mossambicus*)之內部影響濃度(internal effect concentration, IEC)所產生之急性與慢性毒之關係，本研究以毒理動力及動態模擬探討吳郭魚對砷之暴露、累積、作用模態(mode of action, MOA)與所引起毒性之關係。本研究之 7 天生物累積試驗結果顯示吳郭魚主要器官之生物濃縮因子(bioconcentration factor, BCF)皆大於 1 (1.04~3.05)，代表該魚種暴露於含砷水域時具有累積砷之潛力。砷對吳郭魚之急性毒以不同暴露時間下外部半數致死濃度(external median lethal concentration, LC_{50})表示，本研究結果顯示 96 小時 LC_{50} 及 LC_{50} 起始值分別為 28.68 (95% CI: 24.92 ~ 32.44) 及 12.04 μg mL^{-1}。

本研究以關鍵體內濃度(critical body residue, CBR)、關鍵濃度曲線面積(critical area under the curve, CAUC)及損害評估模式(damage assessment model, DAM)等三種以毒理機制為基礎的急性毒模式對吳郭魚暴露於砷之急性毒資料，包括 LC_{50} 及內部半數致死濃度 (internal median lethal concentration, $C_{L,50}$)之描述及預測能力進行評估，進而依據模式理論推論砷對吳郭魚之毒性作用模態。研究結果顯示砷對吳郭魚之急性毒作用方式可以 DAM 模式描述如下：當砷進入魚體後與標的器官內之受體進行可逆之結合，當體內累積損害超過門檻值時將導致生理機能失衡進而導致個體之死亡；而吳郭魚對砷毒性之調節可經由受損組織之修復及吸收與排除速率之調節來進行。因此，本研究建議採用 DAM 模式進行砷對水域生態系之影響評估。

本研究以生理學為基礎之毒理動力(physiologically based toxicokinetic, PBTK)模式探討砷在各器官之生物累積機制，其後並利用此模式預測在不同暴露濃度下

砷在吳郭魚體內之毒理動力行為。本研究並以 IEC 為基礎之希爾方程模式(Hill equation model)結合 DAM 模式建立以標的器官濃度為基礎之劑量-反應關係，並進而依此預測死亡率與暴露時間之關係。研究結果顯示，吳郭魚之鰓對砷毒性較為敏感性可有效作為評估砷毒性之替代器官。

本研究並提出以生物能量學為基礎之架構探討慢性暴露狀態下砷對吳郭魚的成長抑制及作用模態。我們以 28 天的成長暴露試驗進行水體砷濃度與成長抑制程度關係之量化分析。本研究結合以生物能量學為基礎之個體成長模式及動態能量支出模式(dynamic energy budgets, DEB)探討砷之慢性成長毒性。本研究結果顯示吳郭魚之比生長速率(specific growth rate, SGR)與水體砷濃度成反比，我們的成長試驗結果顯示各暴露濃度下所量測到之 SGR 值分別為 0 μg mL^{-1} 時為 0.76 % d^{-1}、1 μg mL^{-1} 為 0.54 % d^{-1}、2 μg mL^{-1} 為 0.26 % d^{-1} 及 4 μg mL^{-1} 為 0.017 % d^{-1}。根據 DEB 理論，本研究指出在食物來源充足之狀態下，砷對吳郭魚成長抑制之作用模態導因於攝食率降低而導致成長率的下降。因此，本研究所建立之以生物能量學及毒性作用模態為基礎之成長模式可以描繪不同暴露條件下吳郭魚從出生至成熟之成長曲線，研究結果顯示在無污染的狀況下吳郭魚之最大成熟體重為 1100.82 g，而當魚體暴露於 1 μg mL^{-1}、2 μg mL^{-1} 及 4 μg mL^{-1} 時其所相對應之值分別為 924.00 g、421.51 g 及 352.13 g。

本論文所建構之以生理學、生物能量學及 IEC 為基礎之評估架構可成功描述不同暴露條件下砷在吳郭魚體內之毒理動力、毒理動態及毒性作用模態。因此，在生態毒理學的研究過程中加入這些因子的考量不僅將促進我們對化學物質毒性的了解，同時亦有助於我們建立更正確的評估模式以減低生態風險評估過程造成疏失的機會，未來並可應用於環境品質規範的制定以保護日益惡化的養殖生

態系統。

關鍵字：砷；生物能量；生態毒理學；內部有效濃度；作用模態；吳郭魚；毒理動力；毒理動態

ABSTRACT

This dissertation proposes a physiologically and bioenergetics based algorithm to relate acute and chronic metal toxicities to the internal effect concentration (IEC) of arsenic (As) in tilapia *Oreochromis mossambicus*. The relationships among As exposure, uptake, accumulation, and toxicity to tilapia are investigated using toxicokinetic (TK) and toxicodynamic (TD) modeling. A 7-d exposure bioassay reveals that the organ-specific bioconcentration factor (BCF) values of tilapia are all above 1 (1.04 – 3.05), indicating that the tilapia is capable of accumulating waterborne As. The As acute toxicity is analyzed by determining the median external effect concentration (LC_{50}) at different integration times, indicating that 96-h LC_{50} and $LC_{50}(\infty)$ for tilapia are 28.68 (95% CI: 24.92-32.44) and 12.04 μg mL^{-1}, respectively.

To determine the mode of action (MOA) governing the As acute toxicity, this study assesses the proposed mechanistics base acute toxicity models, including the critical body residue (CBR) model, the critical area under the curve (CAUC) model, and the recently proposed damage assessment model (DAM). This study test the 3 toxicity models with observed data of tilapia exposed to As, to compare the observed and predicted LC_{50} and median internal effect concentration ($C_{L,50}$). Result suggests that the DAM characterizes As acute toxicity well and indicates that the intrinsic MOA of As toxicity might act through the reversible reaction between As and specific receptors in target sites.

A physiologically based toxicokinetic (PBTK) model is constructed to elucidate the major mechanisms, accounting for the organ-specific selected accumulation of As in tilapia and then utilize the model to predict the behavior of As in tilapia under different exposure scenarios. This study links kinetically DAM with IEC-based Hill

equation model to derive dose-response relationships between equilibrium organ-specific As burdens and mortality effects. Organ-specific dose-response relationships suggest that the gill can be used as a surrogate to assess the As toxicity due to its higher sensibility to toxic effects.

To assess As chronic toxicity to tilapia, a bioenergetics-based approach is presented to analyze effects and the MOA of growth inhibition when tilapia are chronically exposed to waterborne As. A 28-d growth bioassay is conducted to quantitatively determine the relationships between As exposures and the magnitudes of growth inhibition. A bioenergetics-based ontogenetic growth model is incorporated with the DEB_{tox} theory to explore the MOA of As growth toxicity. Result shows that the specific growth rates are inversely proportional to As concentrations and are calculated to be 0.76 % d^{-1} in 0 μg mL^{-1}, 0.54 % d^{-1} in 1 μg mL^{-1}, 0.26 % d^{-1} in 2 μg mL^{-1}, and 0.017 % d^{-1} in 4 μg mL^{-1}, respectively. This study indicates that decreasing of feeding accounts for the As growth inhibition in the case of feeding ad libitum condition. The bioenergetics-based growth model also illustrates the growth trajectories of tilapia in the entire life cycle, suggesting that the maximum biomass of tilapia are 1100.82 g in uncontaminated water, 924.00 g in 1 μg mL^{-1}, 421.51 g in 2 μg mL^{-1}, and 352.13 g in 4 μg mL^{-1}, respectively.

The study shows that the proposed physiologically and bioenergetics-based assessment framework successfully links As exposure to TK and TD under varied exposure scenarios. This study also suggests that considering MOAs in ecotoxicology not only improves our understanding of the toxicities of chemicals but also is useful in setting up models and avoiding pitfalls in species- and site-specific environmental risk assessment. This study also supports the suggestion that replacing external concentrations by IECs is a first step toward a measurement for chemical toxicity and

can be used to improve the construction of future environmental quality criteria programs, aimed at protecting and restoring the rapidly degrading aquacultural ecosystems.

Keywords: Arsenic; Bioenergetics; Ecotoxicology; Internal effect concentration; Mode of action; Tilapia; Toxicokinetics; Toxicodynamics