中文摘要

本研究以台灣西南沿海烏腳病疫區地下水養殖魚類為主要研究對象，檢測分析無機砷在魚體各組織內之生物累積現象及利用生理為基礎之藥理動力及動態學（PBPK/PD）模式模擬魚體內主要器官無機砷之分佈情形、組織內的砷含量，以期求出魚體中各組織內累積砷含量對時間的關係，並預測無機砷濃度變化對魚體之影響。台灣西南沿海地下水含高量無機砷（> 50 ppb），被用來進行養殖；這類地下水養殖魚類均具高經濟價值。本研究於台灣西南部嘉南平原四區（台南縣學甲鎮、北門鄉、嘉義縣義竹鄉、布袋鎮）分別選擇魚類養殖池，長期監測養殖水和魚類（豆仔魚，*Liza macrolepis*及吳郭魚，*Oreochomis sp.*）的砷含量。結果顯示，砷濃度範圍由魚肉的0.98 μg g^{-1}，至腸組織的54.14 μg g^{-1}。魚體含砷量和魚體重量具顯著相關性：吳郭魚體重與砷含量指數關係式，$C_f = 16.801e^{-0.0038W}$（$R^2 = 0.6172, p < 0.05$），豆仔魚體重砷濃度指數關係式$C_f = 83.965e^{-0.0601W}$（$R^2 = 0.7065, p < 0.05$）；式中C_f為魚體中的無機砷含量（μg g^{-1}），W為魚體重量（g）。吳郭魚體重對各組織的含砷量具顯著相關性：以魚體腸、胃、肝組織的砷濃度平均，作為內臟濃度，吳郭魚體重對內臟砷濃度指數關係式，$C_v = 23.274e^{-0.004W}$（$R^2 = 0.6708, p < 0.05$）；吳郭魚肌肉砷濃度大致上與內臟砷濃度成正比關係，$C_v = 3.9378Cm^{0.8134}$（$R^2 = 0.8498, p < 0.05$）。豆仔魚體重對各組織的含砷量亦呈顯著相關性：豆仔魚體重對內臟砷濃度指數關係式，$C_v = 132.5e^{-0.0666W}$（$R^2 = 0.6796, p > 0.05$）。豆仔魚肌肉砷濃度與內臟砷濃度成正比關係，$C_v = 0.9206Cm^{1.7528}$（$R^2 = 0.5049, p > 0.05$）；其中C_m及C_v分別為魚體肉及內臟中無機砷含量（mg g-1）。吳郭魚對砷的穩定生物濃縮因子（BCFss）值為350.28 ± 643.49 mL g^{-1}，豆仔魚則為164.75 ± 298.06 mL g^{-1}，兩者間並無顯著差異（$F = 1.71, p > 0.05$）。

藉由數次野外採樣調查分析結果和動力學理論的推導，發展以生理為基礎之六區塊藥理動力（PBPK）模式；推估無機砷在魚體內主要器官之分佈、各組織內砷含量，並預測無機砷濃度變化對魚體影響之關係。PBPK模式模擬結果顯示暴露於砷環境中300天，砷濃度在魚體含量由高至低依序為：腸12860 ng g^{-1}、肝臟4920 ng g^{-1}、血液4740 ng g^{-1}、胃2320 ng g^{-1}、鰓1470 ng g^{-1}及肌肉1260 ng g^{-1}。模式預測值與野外實測值做模式驗證，結果無論是在肌肉、鰓、胃、腸、及肝臟之含砷量皆極為吻合（平均相對誤差值範圍為4.82 %－81.47 %）；其中雖然腸區塊低估或是胃區塊高估，但模擬曲線皆落在實測值的標準偏差範圍內。

本研究並進行實驗室急性毒實驗以推導藥理動態（PD）模式。急毒實驗結果指出在24, 48, 72, 96小時的半數致死濃度（LC50）分別為69.06 ± 1.66, 51.52 ± 1.74, 38.44 ± 1.83, 及28.68 ± 1.92 μg mL^{-1}。應用急性毒試驗中魚隻死亡率與無機砷濃度關係以Hill模式表示，將不同時間之LC50作為Hill模式中達到最大影響之半致死濃度，結果與無機砷濃度關係做曲線擬合，建構PD模式。整合PBPK與PD模式，進而建構生理為基礎之藥理動力及動態（PBPK/PD）模式。PBPK/PD模式模擬結果可看出累積砷濃度300天造成吳郭魚體致死率影響程度之多寡依序為：腸9.71 %、肝臟0.737 %、血液0.667 %、胃0.092 %、鰓0.026 %及影響最小的肌肉為0.017 % 的致死率。造成魚體致死率影響最為顯著的是腸組織，影響最小則為肌肉。

關鍵詞：魚類；砷；生物累積；生物濃縮因子；生理為基礎之藥理動力及動態模式；烏腳病地區

Abstract

The purposes of this dissertation is to develop a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for arsenic accumulation in aquaculture fish from blackfoot disease (BFD) area, Taiwan. The bioaccumulation of inorganic arsenic (As) in tissues of groundwater aquaculture fish was analyzed. The BFD area is located in the southwest coastal regions of Taiwan in that the aquacultures of the fish located were subjected to As pollution from groundwater. Water and fish (large-scale mullet, *Liza macrolepis* and tilapia, *Oreochomis sp.*) samples were collected from the fish farms in the BFD area of Putai, Yichu, Peimen and Hsuehchia, respectively. The field investigation was to analyze fish for assessing the bioaccumulation of As and to estimate the concentration of As in the aquaculture ecosystems. The equilibrium bioconcentration factors (BCFss) were calculated. Total arsenic concentrations of the aquaculture fish target tissues were analyzed. Results show that As concentrations range from 0.98 μg g^{-1}dry mass in muscle tissue to 54.14 μg g^{-1} in gut tissue. Significant regressions of As in fish (C_f) and in viscera (C_v) against body weight (W) were found , for *O.* sp. : $C_f = 16.801e^{-0.0038W}$ ($R^2 = 0.6172$, $p < 0.05$) and $C_v = 23.274e^{-0.004W}$ ($R^2 = 0.6708$, $p < 0.05$; whereas for *L. macrolepis* : $C_f = 83.965e^{-0.0601W}$($R^2 = 0.7065$, $p < 0.05$)and $C_v = 132.5e^{-0.0666W}$($R^2 = 0.6796$, $p > 0.05$. The BCFss value of As in *O.* sp. was determined to be 350.28 ± 643.49 mL g^{-1}, whereas in *Liza macrolepis* was 164.75 ± 298.06 mL g^{-1}. There was no significant difference ($F = 1.71$, $p > 0.05$) in As concentrations between *O.* sp. and *L. macrolepis*.

The acute toxicity experiment gives the 24- 48- 72- and 96-h LC50 values of 69.06 ± 1.66, 51.52 ± 1.74, 38.44 ± 1.83 and 28.68 ± 1.92 μg mL^{-1}, respectively. The LC50 values obtained from the acute toxicity experiment was incorporated into the Hill model to establish the PD model. A six-compartment PBPK/PD model of the

disposition of As in fish key organs (blood, muscle, gill, stomach, gut, liver) was then developed to predict tissue distributions and to assess effect of As concentration in fish.

A comparison between field observations and model predictions shows that the PBPK/PD model was successfully fitted to determine As concentrations in the target tissues (average % errors range from 4.82 %—81.47 %). After exposing 300 d in As contaminated fish ponds, PBPK/PD model simulations indicate that the order of As concentrations accumulation in fish target tissues is gut (12860 ng g^{-1}) > liver (4920 ng g^{-1}) > blood (4740 ng g^{-1}) > stomach (2320 ng g^{-1}) > gill (1470 ng g^{-1}) > muscle (1260 ng g^{-1}); whereas the order of % mortality is gut (9.71 %) > liver (0.737 %) > blood (0.667 %) > stomach (0.092 %) > gill (0.026 %) > muscle (0.017 %).

***Keywords*:** Fish; Arsenic; Bioaccumulation; Bioconcentration factor (BCFss); Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) model; Blackfoot disease (BFD) area