行政院國家科學委員會專題研究計畫 期中進度報告

砷毒性對吳郭魚之生理毒理動力/動態及作用模態(2/3)
期中進度報告(精簡版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 95-2313-B-002-030-
執 行 期 間 ：95 年 08 月 01 日至 96 年 07 月 31 日
執 行 單 位 ：國立臺灣大學生物環境系統工程學系暨研究所

計 畫 主 持 人：廖中明

報 告 附 件 ：國外研究心得報告

處 理 方 式 ：期中報告不提供公開查詢

中 華 民 國 96 年 06 月 05 日

行政院國家科學委員會專題研究計畫期中報告

砷毒性對吳郭魚之生理毒理動力/動態及作用模態(2/3)

計畫編號：NSC95–2313–B–002–030
執行期限：95/08/01～96/07/31
執行單位：國立台灣大學生物環境系統工程學系
主 持 人：廖中明

摘要

第二年研究重點主要結合毒理動力/毒理動態模式，經由外部效應濃度推求內部效應濃度，研究重點根據第一年實驗數據為基礎，推求砷在吳郭魚體內之毒性最適合之作用模態(MOA)，並且由急性毒模式分析之半致死濃度(LC_{50})，可定量在砷–吳郭魚系統之魚體及特定器官之內部半致死濃度(C_{L50})。結果顯示吳郭魚96小時及無限時間之LC_{50}分別為28.68 (95 %信賴區間介於15.98及47.38) 及25.55 μg mL^{-1}，利用急性毒模式推求發現損害評估模式(DAM)及臨界身體殘餘(CBR)模式可較佳地描述無限時間之LC_{50}值，同時此兩模式推估砷–吳郭魚系統在144小時之LC_{50}均低於觀測值(15.98 μg mL^{-1})。本研究利用Hill方程式預測特定器官劑量與反應之關係，選擇以肝為標的位址之替代品以評估吳郭魚之砷毒性，因為肝對砷具有較高之敏感性。因此當吳郭魚暴露於砷含量小於2 μg mL^{-1}之水域時其預測死亡率不及20%，然而當吳郭魚暴露在砷含量4 μg mL^{-1}下可達70%之預測死亡率。

關鍵詞：生理為基礎之毒理動力/動態模式、內部效應濃度、作用模態、半致死濃度、臨界身體殘餘模式、損害評估模式。

Abstract

The aim of our work (2nd year) was to link physiology based toxicokinetics/toxicodynamics (PBTK/TD) model to estimate the internal effect concentration from external effect concentration. Based on the experimental data obtained from 1st year, we can estimate the suitable mode of action (MOA) for tilapia *Oreochromis mossambicus* exposed to As. Through the lethal concentration (LC_{50}) obtained from acute toxicity model, we could quantify the internal lethal concentration ($C_{L,50}$) for whole body and organ-specific in As–tilapia system. Our results demonstrate that 96-h and incipient LC_{50}s for tilapia are 28.68 (95 % CI: 15.98–47.38) and 25.55 μg mL^{-1}, respectively. Results also show that both of the DAM and CBR models describe the data in an accurate way depending on the estimated incipient LC_{50} values, both of them are lower than the 144-h LC_{50} data (15.98 μg mL^{-1}) in As–tilapia system. We employed the Hill equation model to predict the organ-specific dose–response relationships. We used the liver as a surrogate of target sites to assess the As toxicity to tilapia because of its higher sensitivity to As toxic effects. Hence, the predicted mortalities never reach 20% when the tilapia was exposed to waterborne As < 2 μg mL^{-1}. The predicted mortality, however, reached the 70 % maximum mortality when the tilapia was exposed to 4 μg mL^{-1}.

Keywords: Physiology based toxicokinetics/ toxicodynamics (PBTK/TD) model; Internal effect concentration (IEC); Mode of action (MOA); Lethal concentration (LC_{50}); Critical body residue (CBR) model; Damage assessment model (DAM)

Introduction

Arsenic (As) is widely distributed in water, soil, and organisms from natural and anthropogenic sources. Long-term ingestion of the groundwater contaminated by inorganic As has been found to induce blackfoot disease (BFD) in the southwestern coastal area of Taiwan (Chen et al., 2001). Nowadays, most of the people living in these areas do not drink water from artesian wells because tap water has been made available in this area. However, artesian well water is still used for aquaculture. Farming tilapia (*Orechromis mossambicus*) is one of the most promising aquatic products in the BFD area because of its high market value. Liao et al. (2003) conducted a series of field survey to investigate the As content in pond water and its accumulation in farmed tilapia from BFD area. Their study pointed out that the As concentrations in pond water ranged from 8.1 to 251.7 μg L^{-1} in that As content in several farming ponds persistently exceeds the water quality criteria for total As in the freshwater ecosystems (150 μg L^{-1}) documented by the Criterion Continuous Concentration (USEPA, 2002). If As levels in pond water become high, severe effects may occur on the health of farmed fish, increasing the expenditure of cultivators, and even pose a potential risk to the public who are consume the farmed tilapia from BFD area (Liao and Ling, 2003).

We traditionally employed the environmental concentration as the surrogate for the chemical dose at the target site to produce a given chemical effect to aquatic animals, e.g., the median lethal concentration (LC_{50}) and the lowest observed effect concentration. However, the recently promulgated concept of the body residue hypothesis states that the use of environmental chemical concentrations to gauge hazard could be misleading because the environmental concentration necessary to cause effect varies with the biouptake route, duration of exposure, type of exposure medium, and species used for testing (McCarty and Mackay, 1993). The chemical dose required to induce effects at the target site should not change significantly with routes of

exposure or duration, indicating that the toxicity mechanism does not change and the damage dose does not accumulate over time (McCarty and Mackay, 1993; Sijm et al., 1993; Fisher et al., 1999). Therefore, the target organ/tissue or whole body residue remains an easier and more reliable way of referencing the dose with the continued assumption that the total accumulation reflects the concentration at the target site.

Aquatic animals have been observed in the field to accumulate metals at elevated concentrations in specific organs, such as the liver and intestine, and consequently impose the toxicity of metal to the animals (Labrot et al., 1999; McGeer et al., 2000; Hollis et al., 2001). Understanding this selective accumulation of As into target tissue of tilapia is important in predicting the time variable behavior of As under various exposure conditions. The construction and application of a physiologically based toxicokinetic (PBTK) model of As transfers in tilapia can provide a basis for increasing this understanding. The PBTK models have been developed in several aquatic species in the past years (Nichols et al., 1996; Thomann et al., 1997); however, only a few PBTK models in an aquatic animal have related the toxicological effect to the target organ concentration.

The three specific aims of the second year are (1) to characterize the mode of action dominating the As toxicity to tilapia by validating the proposed acute toxicity models against the dose-time-response data, (2) to develop a mechanistic model based on the mode of action associated with first-order bioaccumulation model to estimate the internal effect concentration (IEC) in target organs of tilapia from LC_{50} data, and (3) to dynamically couple a PBTK/TD model to predict the As distribution and selective accumulation in target organs and to construct dose-response relationships under various exposure scenarios.

Materials and Methods

Mode of action

In the field of aquatic ecotoxicology, several mechanical based acute toxicity models had been proposed to describe the interactions between chemicals and receptors and to quantitatively depict the time course of toxicity. Thus, the toxicokinetic (TK) and toxicodynamic (TD) factors that influence the response of the organism can be examined. Furthermore, these models assumed a first-order TK process to predict the internal median lethal body concentration ($C_{L,50}$) from the time-dependent external median lethal concentration (LC_{50}) data, which are difficult to be detected directly in laboratory experiments and be estimated by statistical analysis techniques.

We will test the proposed models including the critical body residue (CBR) model, the critical area under the curve (CAUC) model, and the damage assessment mode (DAM) by using acute toxicity and bioaccumulation data of tilapia (*Orechromis mossambicus*) exposed to As to compare observed and predicted LC_{50} and then to estimate the time-dependent $C_{L,50}(t)$ of As in tilapia as a function of variables that will be verified with acute toxicity data (**Table 1**). The inherent mechanisms and hypothesis in the acute toxicity models provide the knowledge to assess the As lethal toxicity to tilapia by Hill equation model. **Figure 1** illustrates the principal algorithms and approach phases for using the acute toxicity models and TD-based Hill equation model applied to bioassay analyses.

Arsenic toxicokinetics

In order to represent the principal features of the accumulation and transfer of As in tilapia, a five–compartment model will be constructed (**Figure 2**). The five compartments are blood (#1), carcass (primarily white muscle, skin and skeleton) (#2), gill (#3), alimentary canal (stomach, pyloric caeca, intestine and other viscera) (#4) and liver (#5), respectively.

Mass–balance differential equations describe As uptake by gill from water, delivery by blood to the tissues, distribution into the tissues, metabolism in the tissues, and depuration from the fish into the water. The exchanges between compartments are all assumed to be between dissolved phases of the metal ($\mu g\ g^{-1}$). Thus the mass balance expression for the all compartments (#1) **(Figure 2)** is given by Eq. (10) (**Table 2**). Where Q_{ij} is the diffusive exchange (mL d^{-1}) of dissolved species, f_d is the dissolved fraction of total As concentration in blood, and V_1 is the blood volume (mL). The loss rate from the liver and the alimentary canal was assumed to be a first order to the tissue and whole body weight. The resulting model equations are summarized in **Table 2**.

Model parameterization and validation

The model is composed of terms involving physiological and biochemical parameters. Tissue weights and blood volume can be adapted from our bioaccumulation bioassay. It is not possible to estimate all of the parameters for the model independently of the experimental data because individual experiments for tilapia were not available. It is possible, however, to estimate from the literature, the order of parameters for the exchange rate between compartments and the biochemical parameters including tissue-specific partition coefficient, gill sorption factors and the fraction of As in the blood in the available plasma form.

PBTK model will be validated by the reasonable agreement between the model predictions and data from the concentration–time profiles of As in tissues. The PBTK predictions will be considered to agree with experimentally determined values and field measurements of the concentration-time profiles of As in various organs if they were within one standard deviation of the mean. In addition, the goodness-of-fit was evaluated using root-mean -squared-error (RMSE), computing from RMSE =

Table 1. The summarized equations for proposed acute models

Equation		References
$C_f(t) = BCF_w(1-e^{-k_2 t})$	(1)	CBR model: McCarty and Mackay (1993); Legierse et al. (1999); Lee et al. (2002a); Lee et al. (2002b); Escher and Hermens (2004); Schuler et al. (2004)
$LC_{50}(t) = \frac{C_{L,50}}{BCF(1-e^{-k_2 t})}$	(2)	
$C_{L,50}(t) = LC_{50}(\infty)BCF$	(3)	
$AUC = \int_0^t BCFC_w(1-e^{k_2 t})dt = BCFC_w\left(t - \frac{1-e^{k_2 t}}{k_2}\right)$	(4)	CAUC Model: Legierse et al. (1999); Liao and Lin (2001)
$LC_{50} = \frac{AUC}{BCF}\left(\frac{k_2}{k_2 t + e^{-k_2 t} - 1}\right) + LC_{50}(\infty)$	(5)	
$C_{L,50} = AUC_f\left[\frac{k_2(1-e^{k_2 t})}{k_2 t + e^{k_2 t} - 1}\right] + BCF(1-e^{k_2 t})LC_{50}(\infty)$	(6)	
$D(t) = k_a \frac{k_1}{k_2} C_w\left(\frac{e^{-k_r t} - e^{-k_2 t}}{k_r - k_2} + \frac{1-e^{k_2 t}}{k_r}\right)$	(7)	DAM: Lee et al. (2002b); Schuler et al. (2004)
$LC_{50}(t) = \frac{D_{L,50}/k_a}{\left(\frac{e^{-k_r t} - e^{-k_2 t}}{k_r - k_2} + \frac{1-e^{k_2 t}}{k_r}\right)} BCF^{-1}$	(8)	
$C_{L,50}(t) = \frac{D_{L,50}/k_a}{\left(\frac{e^{-k_r t} - e^{-k_2 t}}{k_r - k_2} + \frac{1-e^{k_2 t}}{k_r}\right)}\left(1-e^{k_2 t}\right)$	(9)	

See text for detailed symbol descriptions.

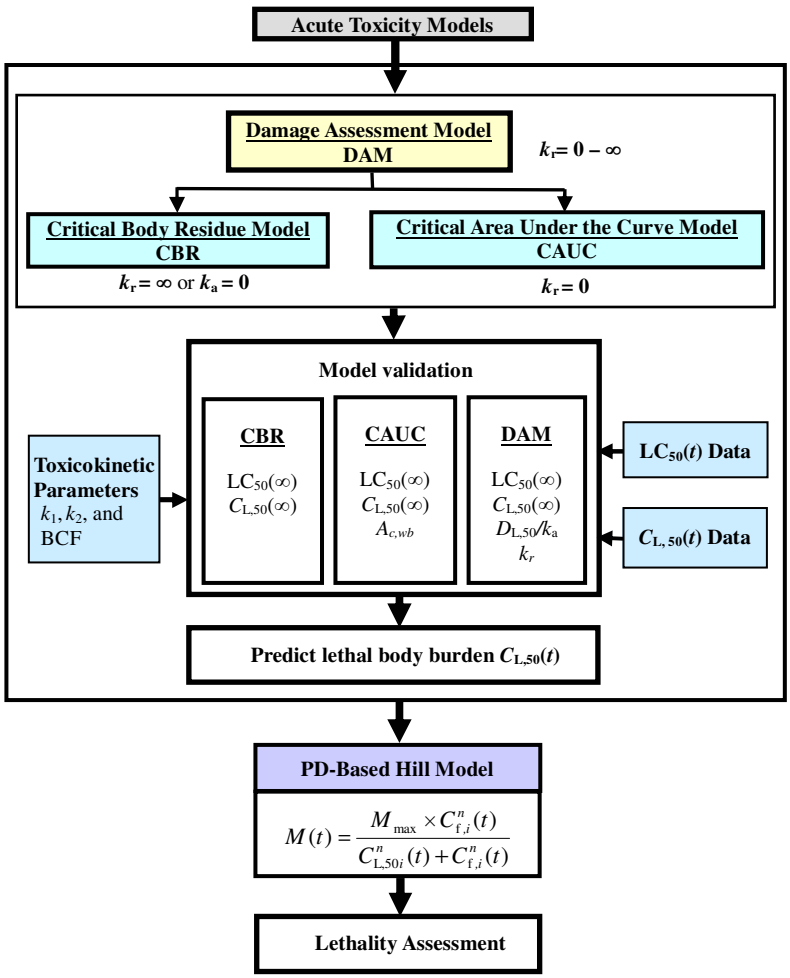

Figure 1. Schematic illustration of the principal algorithms and approach phase for using the acute toxicity models and TD-based Hill equation models applied to bioassay analyses.

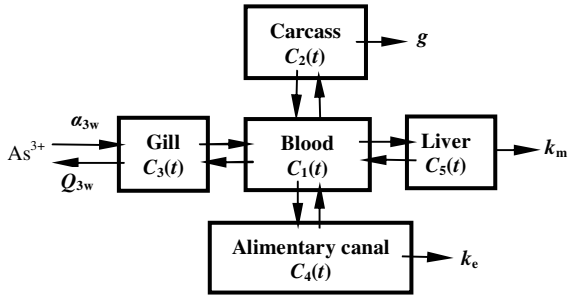

Figure 2. Schematic of five-compartment toxico -kinetic model of tilapia. (The symbols are described in the text.)

$\sqrt{\sum_{n=1}^{N}(C_{m,n}-C_{s,n})^2/N}$ where N denotes the number of measurements, $C_{m,n}$ is the measurement data, and $C_{s,n}$ is the simulation result corresponding to data point n. Our proposed model exercises in Matlab version 5.2 (The Mathworks, Natick, Massachusetts, USA).

Arsenic toxicodynamics

Typically, when assessing the hazard of a chemical to aquatic animals, the bioassays used to estimate the hazard of environmental chemicals in aquatic systems assume that the environmental concentration is

Table 2. PBTK model equations applied to five-compartment of tilapia shown in Figure 1

No.	Compartment	Equation	
1	Blood	$V_1\frac{dC_1}{dt}=Q_{12}\left(\frac{C_2}{\pi_2}-f_dC_1\right)+Q_{13}\left(\frac{C_3}{\pi_3}-f_dC_1\right)+Q_{14}\left(\frac{C_4}{\pi_4}-f_dC_1\right)+Q_{15}\left(\frac{C_5}{\pi_5}-f_dC_1\right)$	(10)
2	Carcass	$w_2\frac{dC_2}{dt}=Q_{21}\left(f_dC_1-\frac{C_2}{\pi_2}\right)-gw_2C_2$	(11)
3	Gill	$w_3\frac{dC_3}{dt}=Q_{31}\left(f_dC_1-\frac{C_3}{\pi_3}\right)+Q_{3w}\left(\alpha_{3w}C_{3w}-\frac{C_3}{\pi_3}\right)$	(12)
4	Alimentary canal	$w_4\frac{dC_4}{dt}=Q_{41}\left(f_dC_1-\frac{C_4}{\pi_4}\right)-k_ew_4C_4$	(13)
5	Liver	$w_5\frac{dC_5}{dt}=Q_{51}\left(f_dC_1-\frac{C_5}{\pi_5}\right)-k_mw_5C_5$	(14)

See text for detailed symbol descriptions.

proportional to the concentration at target site. Thus, with sufficient data over a suitable concentration range, it is possible to calculate best-fit values of three parameters of the TD-based Hill equation model by nonlinear regression (Hill, 1910; Venitz, 1995). The mathematical model used to describe dose-response relationships between mortality and As levels in different target organs of tilapia can be obtained by refining the Hill equation model as

$$M_i=\frac{M_{\max}C_{f,i}^n}{C_{L,50i}^n(\infty)+C_{f,i}^n}=\frac{M_{\max}C_{f,i}^n}{[BCF_iLC_{50}(\infty)]^n+C_{f,i}^n}, \quad (15)$$

where M_i is mortality for target organ i, $C_{f,i}$ is the internal As concentration in target organ i, BCF_i is the bioconcentration factor for target organ i, M_{max} is the tilapia maximum mortality exposed to waterborne As. Based on the acute toxicity test, however, mortality functions were estimated from observed mortality percentages in exposure regimes in which mortality was an increasing function of the As concentration in water rather in target tissue. Therefore, in fitting the Hill equation model to the observed mortality in terms of the specific interval acute toxicity data, the mortality functions was expressed as the functions of waterborne As concentration (C_w) and $LC_{50}(t)$ data as

$$M(t)=\frac{M_{\max}\times C_w^n}{LC_{50}^n(t)+C_w^n} \quad (16)$$

With sufficient data of percent mortality over a range of As concentration in water associated with the specific interval of LC_{50} data, we can estimate best-fit values of the Hill coefficient appeared in Eq. (16) by nonlinear regression.

Results and Discussion

Biokinetic parameters and As toxicity

We had report the toxicokinetic parameters for As calculated from target organs of tilapia exposure data (See the first-year report, NSC94-2811-B-002-041). The 7 d water exposure experiment of As in the gills, liver, alimentary canal, and carcass of tilapia had significant correlated nonlinear regression profiles (r^2 = 0.93–0.96, $p < 0.05$), resulting from the best fit of the first-order one-compartment bioaccumulation model (**Figure 2**). The organ-specific uptake rate constants (k_{1i}) range between 0.12 and 0.84 mL $g^{-1}d^{-1}$. The highest k_{1i} occurs in the alimentary canal, following by the liver, gills, and carcass, respectively. Carcass is the major biomass of tilapia yet shows relative lower uptake ability than other target organs. The depuration rate constants (k_{2i}) range from 0.001 to 0.20 d^{-1}. Our study revealed that the liver and alimentary canal are the organs having the best depuration ability, followed by gills and carcass. All of the organ-specific BCF_i values are above one (1.1–4.2), indicating that these target organs have potential to accumulate As when the tilapia are exposed to waterborne As.

The selected time intervals of 24 h, 48 h, 72 h, 96

h, 120 h, and 144 h LC_{50} values with 95 % CI of As to tilapia are reported (See the first-year report, NSC94-2811-B-002-041). LC_{50} lowers progressively as the duration of exposure increases. A limited number of studies have investigated As toxicity to tilapia. Our 96 h LC_{50}s of As to tilapia is 28.68 (95% CI: 15.98–47.38 μg mL^{-1}), which is close to the range of 96 h LC_{50} of As to seawater tilapia (26.5; 95 % CI: 23.2–33.8 μg mL^{-1}), yet lower than that of to freshwater tilapia (71.7; 95% CI: 67.8– 76.4μg mL^{-1}) reported by Hwang and Tsai (1993).

Fitting toxicity models to $LC_{50}(t)$ data

This study assessed the proposed acute toxicity models which are developed based on different models of toxic action, including the CBR, CAUC, and DAM models (see **Figure 1**), to assess the inherent As toxicity to tilapia by optimal fits of them ti the observed $LC_{50}(t)$ data of As-tilapia system. The estimated model-specific parameters are list in **Table 3**. The average coefficient of determination (r^2, p<0.05) of DAM, CAUC, and CBR models in the two chemical-species combinations are 0.87, 0.78, and 0.87, respectively. The qualitative difference among the fits of the three models are small, which reveals that all of the three models are capable of describing the $LC_{50}(t)$ data. Results show that both of the DAM and CBR models describe the data in an accurate way depending on the estimated incipient LC_{50} values, both of them are lower than the 144-h LC_{50} data (15.98 μg mL^{-1}) in As-tilapia system (**Table 3**).

Organ-specific As toxicokinetics

Figure 3 displays the results of the model prediction comparing with the measured data of the temporal profiles obtained from the 7 d laboratory bioaccumulation bioassay and 300 d real tilapia farms in BFD area, respectively. In general, the PBTK model accurately described As kinetics in the target organs of tilapia. **Table 4** lists the final set of the input parameters used in the PBTK model implementation. **Table 5** lists the RMSE values for the model performances, indicating that each RMSE value is more than 1 SD of the gills, liver, alimentary canal, and carcass during bioaccumulation experiment. The predicted values are within the error limits of the field observations and the RMSE values are more than 1 SD in the liver, as shown in **Table 5**. The simulation results of 300 d field data reveal that the As concentrations in the gills reached steady-state (1.46 μg g^{-1}) in 24 d. The predicted values in carcass approached steady-state condition in 120 d, and they are slightly higher than the measured values, resulting from applying the higher partition coefficient or ignoring some eliminating mechanisms, i.e., elimination by skin, in the model. The estimated blood residue approach steady-state in 120 d (**Figure 3I**), and the residues of As in the blood are higher relative to the liver, gills, and carcass yet similar to alimentary canal, revealing that the blood of tilapia has higher potential to induce As from external medium and connecting tissues.

Predictions of dose-based mortality

A dose–response relationship between equilibrium As concentration in each target organ of tilapia and mortality was predicted by using Eq. (15), and the estimate of Hill coefficient (n) was obtained by optimal fitting of the Eq. (16) to the measure data by nonlinear regression. The optimal fits of Eq. (16) to the observed percent mortality of tilapia versus waterborne As concentration of the 96 h acute toxicity test result in the estimated Hill coefficient, n = 4.07 (r^2 = 0.93, p < 0.05) (**Figure 4A**). Our simulations show that the carcass and liver have relative steep sigmoid dose–response profiles with mortalities approaching 100 %, whereas the gills and alimentary canal have lazy sigmoid dose–response profiles (**Figure 4B**). Therefore, we used the liver as a surrogate of the target site to assess the As lethal toxicity to tilapia because of its higher sensibility to mortality and higher BCF value.

We substituted $C_i(t)$ of the liver obtained from PBTK model and $CL_{50i}(t)$ to obtain the time mortality profiles as functions of toxicokinetic parameters of liver [k_{2i}, BCF_i, and $LC_{50i}(\infty)$] and varied waterborne As concentrations ranging from 1 to 50 μg mL^{-1}. The predicted mortalities by using liver as surrogate target site never reach 50 % when the tilapia are exposed to waterborne As < 2 μg mL^{-1}, which agree with the data of our acute toxicity bioassay (**Figure 5**). The predicted mortality was slightly higher than the observed values before 10 d and reached the 70 %

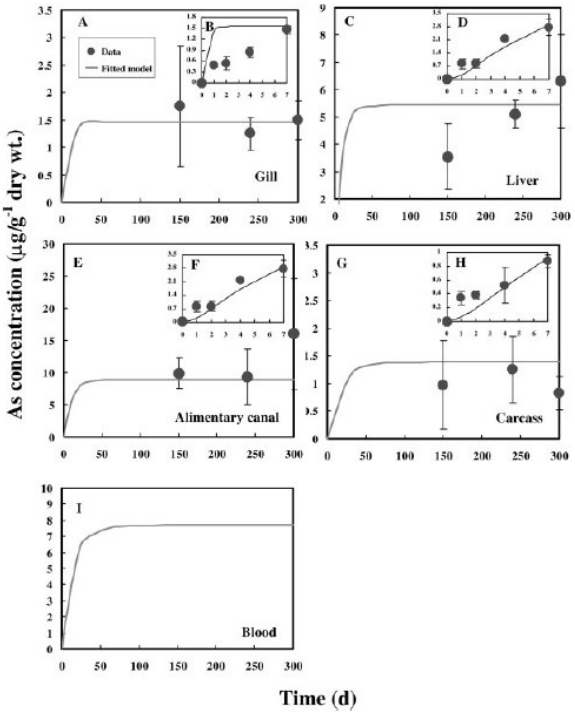

Figure 3. Comparisons of model to measured As concentration (mean ± SD) obtained from 300 day field data (A, C, E, and G) and 7 day laboratory exposure experiment (B, D, F, and H) for the gills, liver, alimentary canal, and carcass. The simulation of blood compartment is also shown (I).

Table 3. Input parameters, parameter estimations and coefficient of determination (r^2) of the optimal fits of the DAM, CAUC, and CBR models to the $LC_{50}(t)$ data

As-tilapia system	DAM	CAUC	CBR
Input Parameters[a]			
k_2 (h^{-1})	0.007	0.007	0.007
BCF (mL g^{-1})	2.88	2.88	2.88
Parameter estimates[b]			
$D_{L,50}/ka$ (μg h g^{-1})	0.5 ± 0.06		
k_r (h^{-1})	68.88 ± 15.33		
$LC_{50}(\infty)$ (μg mL^{-1})	12.04	25.25 ± 5.21	12.04 ± 0.85
AUC (μg h g^{-1})		261.70 ± 67.05	
$C_{L,50}(\infty)$ (μg g^{-1})	34.44	72.72	34.68 ± 2.45
r^2	0.87	0.78	0.87

[a] Determined from 7-day bioaccumulation experiment.
[b] Estimated from $LC_{50}(t)$ data.

Table 4. Physiologically-based parameters used for PBTK model simulation[a]

Symbol	Description	Estimated Value
Physiological parameters		
Q_{3w}	Gill-water exchange rate (mL d^{-1})	10
$Q_{12} = Q_{21}$	Blood-carcass exchange rate (mL d^{-1})	1800
$Q_{13} = Q_{31}$	Blood-gill exchange rate (mL d^{-1})	260
$Q_{14} = Q_{41}$	Blood-alimentary canal exchange rate (mL d^{-1})	3500
$Q_{15} = Q_{51}$	Blood-liver exchange rate (mL d^{-1})	5040
V_1	Blood volume (mL)	2[b]
w_2	Weight of carcass (g)	27.7[b]
w_3	Weight of gills (g)	1.2[b]
w_4	Weight of alimentary canal (g)	0.63[b]
w_5	Weight of liver (g)	0.29[b]
w_t	Whole fish weight (g)	31.8[b]
g	Growth rate (d^{-1})	0.099[c]
k_e	Egestion rate (d^{-1})	0.02
k_m	Liver metabolite rate (d^{-1})	0.0845
Physicochemical parameters		
α_{3w}	Gill sorption factor (-)	8
f_d	Fraction As dissolved in blood	0.2
π_2	Partition coefficient of carcass (mL g^{-1})	2400
π_3	Partition coefficient of gill (mL g^{-1})	50
π_4	Partition coefficient of alimentary canal (mL g^{-1})	1000000
π_5	Partition coefficient of liver (mL g^{-1})	3600
C_w	Water concentration (μg mL^{-1})	94

[a] Calibrated from Thomann et al. (1997) and field observations adopted from Liao et al. (2003).
[b] This study.
[c] Unpublished data.

Table 5. Root-mean-square-error (RMSE) (μg g^{-1}) between measured concentration and simulated concentration in various organs of tilapia

Measured Data	Gill	Liver	Alimentary Canal	Carcass
Bioaccumulation experiment	0.63 (0.15)[a]	0.43 (0.26)	1.22 (0.42)	0.58 (0.15)
Field investigations	021 (0.58)	0.89 (0.87)	0.28 (0.72)	0.20 (0.93)

[a] SD value of bioaccumulation experiment and field investigations.

maximum mortality, which is comparable to the observed data when the tilapia were exposed to 4 and 10 μg mL^{-1} of As.

References

Chen CM, Yu SC, Liu MC. 2001. Use of Japanese medaka (*Oryzia latipes*) and tilapia (*Oreochromis mossambicus*) in toxicity tests on different industrial effluents in Taiwan. Arch Environ Contam Toxicol 40:363–370.

Escher BI, Hermens JLM. 2004. Internal exposure: linking bioavailability to effects. Environ Sci Technol 38:455A-462A.

Fisher SW, Chordas III SW, Landrum PF, 1999. Lethal and sublethal body residues for PCB intoxication in the oligochaete, *Lumbriculus varigatus*. Aquat Toxicol 45:115–126.

Hill AV. 1910. The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. Pro Physiol Soc 40:4–7.

Hollis L, Hogstrand C, Wood CM. 2001. Tissue-specific cadmium accumulation, metallothionein induction, and tissue zinc and copper levels during chronic sublethal cadmium exposure in juvenile rainbow trout. Arch Environ Contam Toxicol 41:468–474.

Hwang PP, Tsai YN. 1993. Effects of arsenic on osmoregulation in the tilapia *Oreochromis mossambicus* reared in seawater. Mar Biol 117:551–558.

Labrot F, Narbonne JF, Ville P, Saint Denis M, Ribera D. 1999. Acute toxicity, toxicokinetics, and tissue target of lead and uranium in the clam *Corbicula fluminea* and the worm *Eisenia fetida*: comparison with the fish Brachydanio rerio. Arch Environ Contam Toxicol 36:167–178.

Lee JH, Peter FL, Koh CH. 2002a. Toxicokinetics and time-dependent PAH toxicity in amphiod *Hyalella azteca*. Environ Sci Technol 36: 3124-3130.

Lee JH, Peter FL, Koh CH. 2002b. Predicition of time-dependent PAH toxicity in *Hyalella azteca* using a damage assessment model. Environ Sci Technol 36:3131–3138.

Legierse KCHM, Verhaar HJM, de Bruijn JHM, Herman JLM. 1999. Analysis of the time-dependent acute aquatic toxicity of organophosphorus pesticides: the critical target occupation model. Environ Sci Technol 33:917–925.

Liao CM, Chen BC, Singh S, Lin MC, Liu CW, Han BC. 2003. Acute toxicity and bioaccumulation of arsenic in tilapia (*Oreochromis mossambicus*) from a blackfoot disease area in Taiwan. Environ Toxicol 18:252–259.

Liao CM, Lin MC. 2001. Acute toxicity modeling of rainbow trout and silver sea bream exposed to waterborne metals. Environ Toxicol 16:349-360.

Liao CM, Ling MP. 2003. Assessment of human health risk for arsenic bioaccumulation in tilapia (*Oreochromis mossambicus*) and large-scale mullet (*Liza macrolepis*) from blackfoot disease area in Taiwan. Arch Environ Contam Toxicol 45:264–272.

McCarty LS, Mackay D. 1993. Enhancing ecotoxicological modeling and assessment. Environ Sci Technol 9:1719–1728.

McGeer JC, Szebedinszky C, McDonald DG, Wood CM. 2000. Effects of chronic sublethal exposure to waterborne Cu, Cd or Zn in rainbow trout 2: tissue specific metal accumulation. Aquatic Toxicol 50:245–256.

Nichols JW, McKim JM, Lien GJ, Hoffman AD, Bertelsen SL, Elonen CM. 1996. A physiologically based toxicokinetic model for dermal absorption of organic chemicals by fish. Fundam Appl Toxicol 31:229–242.

Sijm DTHM, Part P, Opperhuizen A. 1993. The influence of temperature on the uptake rate constants of hydrophobic compounds determined by the isolated perfused gills of rainbow trout (*Oncorhynchus mykiss*). Aquatic Toxicol 25:1–14.

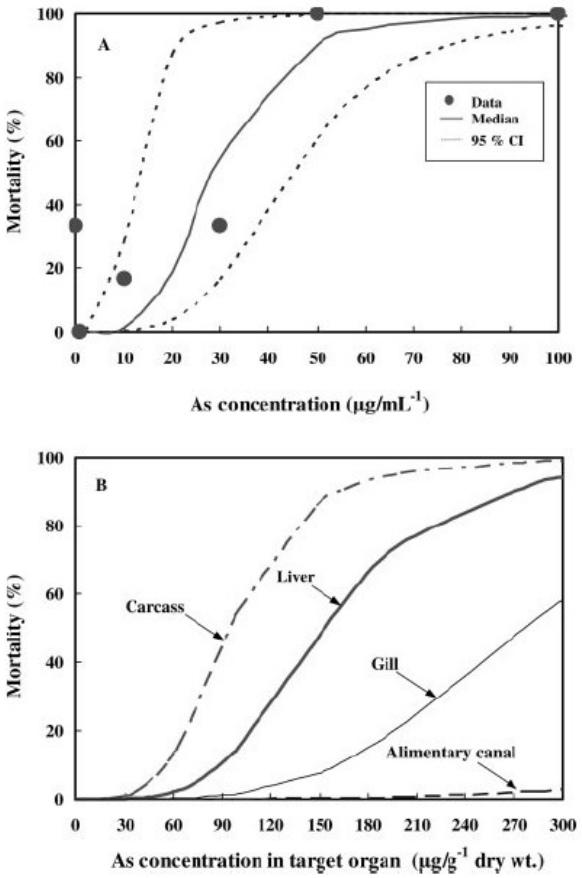

Figure 4. (A) Optimal fit of Hill equation model to the observed percent mortality of tilapia versus waterborne As concentration in the acute toxicity bioassay with 95 % CI, where the 96 h LC_{50} is 28.68 (95 % CI: 15.98-47.38) and (B) derived organ-specific dose-response relationships between equilibrium internal effect concentration of As and mortality effects for tilapia *O. mossambicus*.

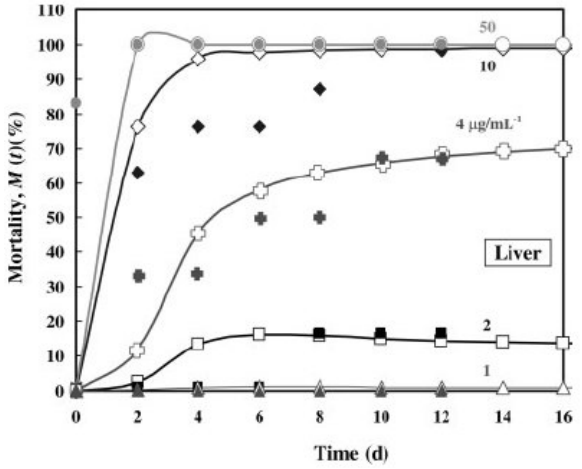

Figure 5. Prediction of time-mortality of tilapia exposed to waterborne As, ranged from 1 to 50 μg mL^{-1}, by using the liver as a biomarker. Solid symbols are the measured data from the acute toxicity bioassay, and the corresponding open symbols are the predicted values from Eq. (16).

Schuler LJ, Landrum PF, Lydy MJ. 2004. Time–dependent toxicity of fluoranthene to freshwater invertebrates and the role of biotransformation on lethal body residues. Environ Sci Technol 38:6247-6255.

Thomann RV, Shkreli F, Harrison S. 1997. A toxicokinetic model of cadium in rainbow trout. Environ Toxicol Chem 16:2268–2274.

USEPA, 2002. National recommended water quality criteria: 2002. EPA-822-R-02-047. Available at: http://www.epa.gov/ost/pc/revcom.pdf.

Venitz J. 1995. Toxicokinetic-toxicodynamic modeling of reversible drug effects. In: Derendorf H, Hochhaus G, editors. Handbook of Toxicokinetic/Toxicodynamic Correlation. Boca Raton, FL: CRC Press. p 1–34.

行政院國家科學委員會補助國內專家學者出席國際學術會議報告

96 年 6 月 5 日

附件三

報告人姓名	廖中明	服務機構及職稱	國立台灣大學 生物環境系統工程所教授
時間 會議 地點	20-24 May 2006 Porto, Portugal	本會核定 補助文號	NSC95-2313-B-002-030
會議名稱	(中文) 環境毒理與化學國際研討會 (英文) Society of Environmental Toxicology and Chemistry (SETAC)		
發表論文題目	(中文) 以生物動力與韋伯分佈為基礎之流病架構評估砷之安全攝食量及其健康效應 (英文) A biokinetic and Weibull-based epidemiological framework for assessing safe arsenic intake and health effects		

報告內容應包括下列各項：

一、參加會議經過

第十七屆 SETAC 歐洲國際會議共計五天議程於葡萄牙(波多)舉行，會場位於波多會議中心。此會議包含十大類環境相關主題，分別為 Climate Changes, Environmental Chemistry, Environmental Risk Assessment, Ecotoxicology and Stress Ecology, Life Cycle Assessment (LCA), Mechanisms of Toxicity, Pollution and Human Health Effects, From Finding to Regulation: Political and Socio Economic Aspects of Environmental Issues, Tropical Ecotoxicology, and Special Topics Symposium。本人所投稿的議題屬於 Pollution and Human Health Effects: Polluted drinking water and human health 範疇，於五月二十三日下午五點三十分至五點五十五分以海報方式呈現。與會者多為歐洲各國學者，內容多探討重金屬與有機化合物的環境污染問題，及評估安全飲用水之標準制定，期間與各國學者互有討論及彼此交換研究心得。

二、與會心得

本次所舉辦的國際研討會，本人給予相當正面的評價，整題規劃可看出舉辦單位之用心，如海報展示區標示清楚，現場亦提供了學者討論的場地與空間。與會後對於本人未來的研究方向，擬出三大點：(1) Climate change issues, (2) Aquatic animal health, (3) Nanoparticles exposure toxicology.

三、考察參觀活動(無此項活動者省略)

無

四、建議

無

五、攜回資料名稱及內容

1. SETAC 第十七屆歐洲會議簡介 (包括各議程投稿作者與題目)
2. SETAC 會議光碟
3. 相關研究領域且有興趣之海報影本

六、其他

ABSTRACT (WE PC8-2)

A biokinetic and Weibull-based epidemiological framework for assessing safe arsenic intake and health effects

Chung-Min Liao, Huan-Hsiang Shen, Tzu-Ling Lin, Szu-Chieh Chen, Chi-Ling Chen, Lin-I Hsu, Chien-Jen Chen
National Taiwan University, TAIPEI, Taiwan

Ingested inorganic arsenic is strongly associated with a wide spectrum of adverse health outcomes. We propose a biokinetic and Weibull model-based epidemiological framework to accurately estimate the safe arsenic intake guideline for tilapia consumption and safe tilapia cultured water arsenic standard based on biokinetics of tilapia and gender/age/cancer-specific epidemiological data in arseniasis-endemic area in Taiwan. The present arsenic epidemiology is based on an 8 years follow-up study of 10,138 residents in arseniasis-endemic areas in southwestern and northwestern Taiwan. Here we adopt 0.01% and 1% excess lifetime cancer risk based point-of-departure analysis to quantify the risk estimates. We perform excess cancer risk assessment by the Monte Carlo simulation technique. Our results show a positive relationship between arsenic exposure and age/gender- and cancer-specific cumulative incidence rate using Weibull dose-response model. Based on male bladder cancer with an excess lifetime cancer risk of 10-4, we estimate the safe tilapia cultured water inorganic arsenic guideline value to be 45 mg/L that meets reasonably well with the regulatory authorities recommended guideline of 50 mg/L. Our findings show that consumption of tilapia in blackfoot disease (BFD)-endemic area poses no significant cancer risk (excess cancer risks ranging from 2.0x10-5 6x10-5), implicating that peoples in BFD-endemic area are not readily associated with higher fatalities for bladder cancer exposed from tilapia consumption. We are confident that our model can be easily adapted for other aquaculture species and encourage risk managers to use the model to evaluate the potential population-level long-term low dose cancer risks. We conclude that, by understanding the linkages between biokinetics of tilapia and arsenic epidemiology of human-arsenic-tilapia interactions, we can provide a scientific basis for risk analysis to enhance broad risk management strategies.