

A Human PBPK/PD Model to Assess Arsenic Exposure Risk Through Farmed Tilapia Consumption

M.-P. Ling · C.-M. Liao

Received: 20 November 2008 / Accepted: 30 April 2009 / Published online: 19 May 2009
© Springer Science+Business Media, LLC 2009

Abstract The purpose of this study was to develop a biologically based risk assessment model for human health through consumption of arsenic (As) contaminated farmed tilapia (*Oreochromis mossambicus*) from blackfoot disease (BFD)-endemic area in Taiwan for estimating the consumption advice. We linked a physiologically based pharmacokinetic (PBPK) and a pharmacodynamic (PD) model to account for the exposure and dose-response profiles of As in human. Risk analysis indicates that consumption of farmed tilapia poses no significant threat from As-induced lung and bladder cancers. The predicted risk-based median consumption advice was no more than 5–17 meals month⁻¹ (or 2–6 g day⁻¹).

Keywords Arsenic · PBPK/PD · Risk analysis · Consumption advice

Arsenic (As) is a common environmental toxicant and a known human carcinogen. Tseng et al. (2007) indicated that long-time exposure to ingest inorganic As in groundwater has been found to induce blackfoot disease (BFD). BFD is a unique peripheral vascular disease that ends with dry gangrene and spontaneous amputation of affected extremities in a limited area on the southwest coast of

Taiwan. Nowadays, most of the people living in these areas do not drink groundwater. However, groundwater is still used for aquaculture. Farming of tilapia (*Oreochromis mossambicus*) is a promising business at BFD-endemic area in Taiwan. Agency for Toxic Substances and Disease Registry (ATSDR) (2000) indicated that ingestion of As may increase the risks of internal cancers. ATSDR (2000) further noted the occurrence of internal tumors of the internal tissues in patients with As-induced skin cancer. However, the USEPA has not yet calculated a specific risk value or cancer slope factor for As-induced internal cancers (ATSDR 2000). In this study, we developed a risk model that linked a physiologically based pharmacokinetic (PBPK) model and a pharmacodynamic (PD) model. The PBPK model can estimate As exposure distributions in human blood, lung, bladder, skin, and GI tract. The PD model can be used to reconstruct dose-response functions for arsenicosis (hyperpigmentation and keratosis) and As-induced cancers (lung, bladder, and skin cancers). We combined the exposure distribution profiles and the reconstructed dose-response profiles to predict and to compare the human As exposure risks for subsistence fishers in BFD-endemic area and residents in non-BFD-endemic area in Taiwan region.

The purposes of this study were: (1) to conduct a biologically-based risk assessment based on the USEPA (1998) methodology for human As exposure risk through consumption of farmed tilapia from BFD-endemic area in Taiwan; (2) to address the uncertainties by using a probabilistic PBPK/PD approach to characterize risks that yield quantitative risk estimates and their associated uncertainties; and (3) to estimate risk-based consumption advice regarding As contaminated farmed tilapia based on USEPA (2000) approach for potential carcinogenic risks.

M.-P. Ling (✉)
Department of Health Risk Management, China
Medical University, Taichung 40402, Taiwan,
ROC
e-mail: lingmp@mail.cmu.edu.tw

C.-M. Liao
Department of Bioenvironmental Systems Engineering,
National Taiwan University, Taipei 10617, Taiwan, ROC

Materials and Methods

The pathway of As exposure for human is through farmed tilapia consumption. Farmed tilapia is contaminated with

organ i , $\{u(t)\}$ represents an input vector of chemical concentration in tilapia muscle, $[K]$ is a state matrix describes the diffusion exchange rate between target organs,

$$[K] = \begin{bmatrix} -(Q_L + Q_{BL} + Q_S + Q_{GI})\frac{F_D}{V_B} & \frac{Q_L}{R_L V_B} & \frac{Q_{BL}}{R_{BL} V_B} & \frac{Q_S}{R_S V_B} & \frac{Q_{GI}}{R_{GI} V_B} \\ \frac{Q_L F_D}{W_L} & -\left(\frac{Q_L}{R_L W_L}\right) & 0 & 0 & 0 \\ \frac{Q_{BL} F_D}{W_{BL}} & 0 & -\left(\frac{Q_{BL}}{R_{BL} W_{BL}} + K_U\right) & 0 & 0 \\ \frac{Q_S F_D}{W_S} & 0 & 0 & -\left(\frac{Q_S}{R_S W_S}\right) & 0 \\ \frac{Q_{GI} F_D}{W_{GI}} & 0 & 0 & 0 & -\left(\frac{Q_{GI}}{R_{GI} W_{GI}} + K_F\right) \end{bmatrix},$$

As through groundwater. Exposures of subsistence fishers in BFD-endemic area and residents in non-BFD-endemic area to As were only through consumption of farmed tilapia obtained from tilapia farms in BFD-endemic area. We assumed people only eating the muscle part of contaminated farmed tilapia. The As level in farmed tilapia muscle is determined by using a physiologically based toxicokinetic (PBTK) model (Ling et al. 2005). In this

and $[X]$ is a constant input matrix describes the exchange rate into the target organ,

$$[X] = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{CRz}{W_{GI}} \end{bmatrix}^T.$$

We considered the steady-state condition in Eq. 1 and respectively solved for the steady-state As concentrations in human lung (C_L), bladder (C_{BL}), and skin (C_S),

$$C_L = \frac{Q_L F_D I J C G}{[A F H I J - (H I J B Q_L F_D + F I J C Q_{BL} F_D + F H J D Q_S F_D + F H I E Q_{GI} F_D)]}, \tag{2}$$

$$C_{BL} = \frac{Q_{BL} F_D F I C G}{[A F H I J - (H I J B Q_L F_D + F I J C Q_{BL} F_D + F H J D Q_S F_D + F H I E Q_{GI} F_D)]}, \tag{3}$$

$$C_S = \frac{Q_S F_D F J C G}{[A F H I J - (H I J B Q_L F_D + F I J C Q_{BL} F_D + F H J D Q_S F_D + F H I E Q_{GI} F_D)]}, \tag{4}$$

study, the inorganic As level is account for 7.4% of the total As in farmed tilapia from BFD-endemic area (Huang et al. 2003).

We used a PBPK model to simulate inorganic As accumulation in human target organs through farmed tilapia muscle consumption. Our PBPK model structure consists of lung (compartment 2), bladder (compartment 3), skin (compartment 4), and GI tract (compartment 5), which were interconnected by blood (compartment 1) circulation. The present PBPK models can be described by a linear dynamic equation (Yu 1998, 1999a, b),

$$\frac{d\{C_{H,i}(t)\}}{dt} = [K]\{C_{H,i}(t)\} + [X]\{u(t)\}, \tag{1}$$

where $\{C_{H,i}(t)\}$ is a state variable vector which describes the chemical concentration in each assigned human target

where $A = F_D(Q_L + Q_{BL} + Q_S + Q_{GI})$, $B = Q_L R_L^{-1}$, $C = Q_{BL} R_{BL}^{-1}$, $D = Q_S R_S^{-1}$, $E = Q_{GI} R_{GI}^{-1}$, $F = Q_L R_L^{-1} + K_H W_L$, $G = CR\alpha C_{F,m}$, $H = Q_{GI} R_{GI}^{-1} + CR\alpha K_F T$, $I = Q_S R_S^{-1} + K_S B W$, and $J = Q_{BL} R_{BL}^{-1} + K_U W_{BL}$, in that $C_{F,m}$ is the As concentration in tilapia muscle ($\mu\text{g g}^{-1}$); Q_i is the diffusive exchange rate of organ i (L day^{-1}); F_D is the binding coefficient of As concentration to plasma proteins (g L^{-1}); R_i defines as C_i/C_{di} , which denotes the partition coefficient or is referred to as an organ/blood equilibrium distribution ratio for linear binding in specific organ i (L g^{-1}) in that C_i is the total As concentration in human target organ i ($\mu\text{g g}^{-1}$) and C_{di} is the dissolved As concentration in the blood leaving target organ i ($\mu\text{g mL}^{-1}$); V_B is the blood volume (L); CR is the daily tilapia muscle consumption rate (g day^{-1}); W_L , W_{BL} and W_{GI} are the organ weight of lung, bladder and GI tract (g),

respectively; BW is the consumer body weight (kg); α is absorption efficiency of As (%); T is time to 95% steady state in GI tract (days); K_H is the respiration rate ($\text{g g}^{-1} \text{day}^{-1}$); K_U is the urine elimination rate ($\text{g g}^{-1} \text{day}^{-1}$); K_S is the sweat elimination rate ($\text{g g}^{-1} \text{day}^{-1}$) and K_F is the fecal elimination rate ($\text{g g}^{-1} \text{day}^{-1}$). The respiration rate and sweat elimination rate are much less than the elimination rate in bladder and GI tract. Hence, we ignored the respiration rate and sweat elimination rate (Table 1).

Dose-response functions for morbidity and fatality effects versus As level in target human organs were fitted by using a empirical three-parameter Hill equation based PD model to the previously published dose-response functions of the quadratic-exponential for arsenicosis and

As-induced cancers based on epidemiological data from West Bengal and Taiwan (Yu et al. 2003). The reconstructed dose-response profiles for given organ-specific As concentration in human, $P(E_i|C_{H,i})$ could be expressed as conditional cumulative distribution function (cdf),

$$P(E_i|C_{H,i}) = \Phi\left(\frac{E_{\max} \times C_{H,i}^n}{EC_{50,i}^n + C_{H,i}^n}\right), \quad (5)$$

where $C_{H,i}$ is the internal As concentration in human target organ i ($\mu\text{g g}^{-1}$), E_i is human prevalence or incidence of those exposed to As through farmed tilapia consumption, E_{\max} is human maximum prevalence or incidence that assumed values were 100%, $EC_{50,i}$ is the 50% effect

Table 1 Input parameters values for human used for PBPK model simulation

Parameters	Symbol	Value
<i>Physiological parameters for human</i>		
Blood perfusion rate (L day^{-1}) ^a		
Lung	Q_L	230.4
Bladder	Q_{BL}	1,368
Skin	Q_S	504.0
GI tract	Q_{GI}	1,382.4
Partition coefficient (L g^{-1}) ^b		
Lung: blood	R_L	4.15
Bladder: blood	R_{BL}	4.15
Skin: blood	R_S	2.5
GI tract: blood	R_{GI}	2.5
Fraction As dissolved in blood (g L^{-1}) ^c	F_D	0.2
Time to 95% steady state in GI tract (days) ^d	T	1
Absorption efficiency of As (%) ^e	α	35
Body weight (kg)	BW	$N(60.55, 4.67)$ ^f
Bladder weight (g)	W_{BL}	$N(268.78, 26.88)$ ^g
Daily tilapia consumption rate (g day^{-1})		
Subsistence fishers (2–6 meals week ⁻¹) in BFD-endemic area ^h	CR_{2-6}	$LN(22.07, 2.61)$
Subsistence fishers (7–14 meals week ⁻¹) in BFD-endemic area ^h	CR_{7-14}	$LN(36.68, 1.75)$
Residents (average tilapia consumption rates) in Taiwan ⁱ	CR_{average}	$LN(10.26, 1.10)$
Meal size for human eating tilapia (g meal^{-1}) ^j	MS	$LN(10.26, 1.10)$
<i>Biokinetic parameters^k</i>		
Urine elimination rate (day^{-1})	K_U	$LN(1.79, 1.10)$
Fecal elimination rate (day^{-1})	K_F	$LN(0.029, 1.11)$
<i>Chemical parameter^l</i>		
As concentration in tilapia muscle ($\mu\text{g g}^{-1}$)	$C_{F,m}$	$LN(0.52, 2.60)$
<i>Dose-response parameters</i>		
Median effective concentration ($\mu\text{g g}^{-1}$) ^m		
Hyperpigmentation	$EC_{50,\text{Hyper}}$	$N(4.593, 1.197)$
Keratosi	$EC_{50,\text{Ker}}$	$N(6.360, 0.883)$
Skin cancer	$EC_{50,\text{SC}}$	$N(4.647, 0.361)$
Lung cancer	$EC_{50,\text{LC}}$	$N(222.0, 56.569)$
Bladder cancer	$EC_{50,\text{BC}}$	$N(470.0, 31.113)$

Table 1 continued

Parameters	Symbol	Value
Cancer slope factor correction [(mg kg ⁻¹ day ⁻¹) ⁻¹] ^a		
Lung cancer	<i>CSF_{corr,LC}</i>	N(9.43, 1.30)
Bladder cancer	<i>CSF_{corr,BC}</i>	N(2.77, 0.37)

^a Values were taken from Mann et al. (1996) and Leggett (2003)

^b Values were taken from Yu (1999a)

^c Adopted from Leggett et al. (2003)

^d Estimated from Lawrence and Gobas (1997)

^e Adopted from Lung et al. (2003)

^f Information adopted from Department of Health, Taiwan (2006) (19–65 years)

^g Value was taken from Mann et al. (1996)

^h Values were adapted from Lin (unpublished work), which were based on a questionnaire from 57 subsistence fishers in BFD-endemic area for 2–6 and 7–14 meals week⁻¹, respectively

ⁱ Value was calculated from annual consumption quantities of tilapia by the number of residents (age > 5 years) in Taiwan (Department of Statistics 2006, Fisheries Administration 2006)

^j Value was assumed the same average tilapia consumption rates of residences in Taiwan

^k Values were taken from Yu (1999b)

^l Values were taken from Ling et al. (2005)

^m The reconstructed distributions derived from published dose-response functions (Yu et al. 2003)

ⁿ Values taken from the upper 95% CI on the linear term in the multistage model, based on an assumed 1 meal tilapia consumed per day as suggested by USEPA (2000)

concentration (µg g⁻¹) of the *E_{max}*, *n* is the Hill coefficient which is a measure of cooperativity, and $\Phi(\bullet)$ is the cumulative standard normal distribution.

Risk at a specific As concentration in human target organ in a joint probability function or exceedence profile, which describes the probability of exceeding the concentration associated with a particular degree of effect. This can be expressed mathematically as

$$P(R_{C_{H,i}}) = P(C_{H,i})P(E_i|C_{H,i}), \tag{6}$$

where $P(R_{C_{H,i}})$ is the risk for a specific organ *i* at concentration *C_{H,i}*, and $P(C_{H,i})$ is the cdf of having organ concentration *C_{H,i}*.

We predicted the consumption advice for As based on estimates of potential carcinogenic risks and on an assumption of risk activity (USEPA 2000). To calculate meal consumption limits based on a contaminant’s carcinogenic effects, the first step is the calculation of daily consumption limits and is defined as (USEPA 2000)

$$CR_{lim,carcinogenic} = \frac{ARL \cdot BW}{CSF_{corr} \cdot C_{F,m}}, \tag{7}$$

where *CR_{lim}* is the maximum allowable tilapia consumption rate (g day⁻¹), *BW* is the consumer body weight (kg), *ARL* = 10⁻⁵ is the maximum acceptable individual lifetime risk level suggested by USEPA (2000) (unit less), and *CSF_{corr}* is a corrected cancer slope factor for the dose-response function [(mg kg⁻¹ day⁻¹)⁻¹]. The

second step is the calculation of meal consumption limits and is defined as (USEPA 2000)

$$CR_{mm,carcinogenic} = \frac{CR_{lim,carcinogenic} \cdot T_{ap}}{MS}, \tag{8}$$

where *CR_{mm}* is the maximum allowable tilapia consumption rate (meals month⁻¹), *MS* is the meal size for human eating tilapia (g meal⁻¹), and *T_{ap}* is the time averaging period (365.25 days 12 months⁻¹ = 30.44 days month⁻¹ (USEPA 2000)).

The data of amount of tilapia consumed by subsistence fishers in BFD-endemic area and residents in Taiwan were collected in 2004 and 2006, respectively. Data on tilapia consumption in subsistence fishers in BFD-endemic area in 2004 were adapted from Lin (Nanhua University, Chiayi, Taiwan, unpublished data), which was based on a questionnaire from 57 subsistence fishers. Data of tilapia consumption by residents in Taiwan was calculated from the reports of Fisheries Administration (2006) and Department of Statistics (2006). We divide the annual consumption quantities of tilapia by the number of residents (age > 5 years) in Taiwan. These data were the newest among available literature. In order to provide an estimate for each of the model parameters, Monte Carlo (MC) analysis was performed to generate the probability distributions. The chi-square (χ²) and Kolmogorov–Smirnov (K–S) goodness-of-fit were used to determine the optimal fitted distributions for MC simulation (Table 1). Data and distribution parameters were analyzed and

estimated using the Statistica® software (Version 7.1, StatSoft, Tulsa, OK, USA). A sensitivity analysis was performed to identify and determine the most significant parameters influencing the value that presented in the uncertainty and variability analysis. The result shows that 10,000 iterations are sufficient to ensure the stability of results. We incorporate probability distributions into MC simulation to obtain 2.5%- and 97.5%-tiles as 95% confidence interval (CI) for all uncertainty analyses. The Crystal Ball® software (Version 7.3, Decisioneering, Inc., Denver, Colorado, USA) was used to perform all the MC simulations.

Results and Discussion

Figure 1 depicts the exposure profile of the box and whisker plot and the exceedence risk functions with 95% CI with noncarcinogenic and carcinogenic effect based on different tilapia consumption rates. The comparison of 90%-tile values shows that human exposure to As caused the relative skewness and spread in modeled output varied among specific organs. Our results demonstrate that the distribution of As concentration in human bladder is more highly skewed with a long tail at higher concentration (Fig. 1).

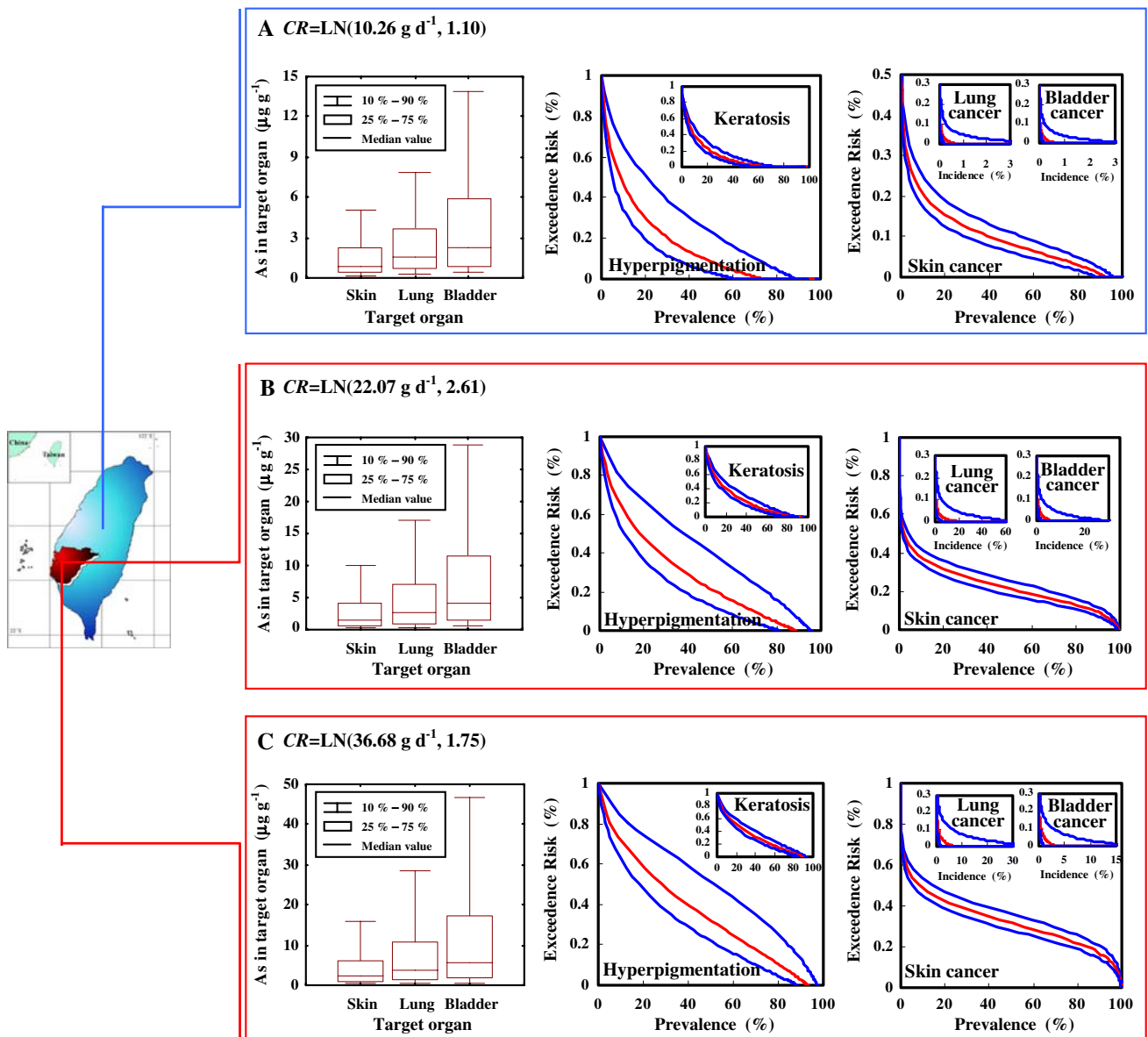


Fig. 1 Box and whisker plot representations of distributions of As concentration in human target organ and exceedence risk functions with 95% CI in noncarcinogenic effects: hyperpigmentation,

keratosis, and carcinogenic effects: skin cancer, lung cancer, and bladder cancer according to tilapia consumption rates (CR) of a residents in Taiwan and b, c subsistence fishers in BFD-endemic area

We optimal fitted the Hill model to published dose-response functions to obtain the reconstructed dose-response profiles from Eq. 5 for arsenicosis and As-induced cancers. The Hill model and a 10,000 MC simulation provided an adequate fit for the data (χ^2 goodness-of-fit, $p > 0.5$). The n and EC_{50} values clearly show that there were significant differences in sensitivity to As in different human health effects. Regression analyses show that the nonlinear Hill three-parameter model in a good agreement with published dose-response models as judged by high r^2 values (0.972–0.999, $p < 0.05$). The Hill coefficients (n) for arsenicosis (1.344–1.402) and for As-induced cancers (3.206–3.474) are indicative of positive cooperativity.

Exceedence risk functions shown in Fig. 1 were based on the exposure and dose-response profiles for human consumption of farmed tilapia. Because of variability and uncertainty in model parameters from Eq. 6 describing the exceedence cdfs associated with a particular degree of prevalence and incidence, we applied the plotted probabilities calculated from the outcome of the MC simulation to estimate risks. For skin cancer from subsistence fishers ($CR = LN(22.07 \text{ g day}^{-1}, 2.61)$) in BFD-endemic area, the probabilities that 10% or more of human affected (risk = 0.10) is approximately 88% (95% CI: 81%–93%). Therefore, the probability is 0.10 for at least 88% of human will be affected; whereas the probability is 0.5 for at least 2% (95% CI: 1%–4%) of human will pose health risks (Fig. 1b). Overall, risk diagrams (Fig. 1) demonstrate that consumption of farmed tilapia from BFD-endemic area may increase potential prevalence ratios of arsenicosis and skin cancer, yet pose no significant threat to health risks from lung and bladder cancers.

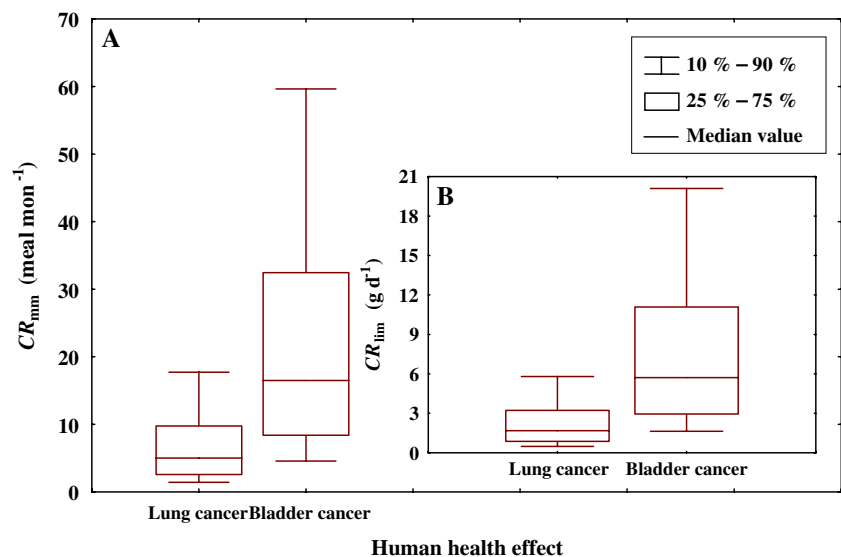
We recommended that the toxicological effect resulting in the more conservative consumption limits can be used to

estimate an advisory since resulting limits would be protective of cancer health effects. Figure 2 shows the recommended consumption limit of tilapia from BFD-endemic area in daily (g day^{-1}) and meal (meals month^{-1}) basis for adults in Taiwan, suggesting a median meal consumption rate for lung and bladder cancer effects of 5 to 17 meals month^{-1} (Fig. 2a) or 1.68 and 5.72 g day^{-1} , respectively (Fig. 2b). Our finding also indicates that the As-induced lung and bladder cancer risks generally considered a low individuals exposing risk in eating contaminated farmed tilapia of the people. This advice for human carcinogenicity health effects is more restrictive than consumption advice triggered contaminants in the tissues of farmed tilapia.

Sensitivity analysis indicates that the most important exposure variable for As in human organ-specific is As concentration in tilapia muscle. The contribution is approximately 54.1%. Arsenic concentration in human organ is the key parameter for estimating human organ-specific dose-response relationships. For allowable maximum consumption advice for As, the key parameter in the tilapia consumption limits is As concentration in tilapia muscle that contribution to variance is approximately 100%.

In conclusion, this study indicates that consumption of As contaminated farmed tilapia may pose potential arsenicosis and skin cancer risks, yet pose low risks to human health risks from As-induced internal cancers. To precise determine the risk/benefit ratios from consumption of farmed tilapia are complicated, cautious interpretation of present data may substantially reduce the likelihood in dealing with uncertainty and risk management. This present probabilistic risk scheme provides general conclusions that are more robust than estimates made without probabilistic presentations of outcomes.

Fig. 2 Risk-based consumption advisories for human As-induced lung and bladder cancer effects with maximum allowable tilapia consumption rates for **a** meal limits for consumption rate of tilapia (CR_{mm}), and **b** daily limits for consumption rate of tilapia (CR_{lim})



Acknowledgments This study was funded by the National Science Council of Republic of China (NSC 96-2313-B-039-001-MY2) and China Medical University (CMU 96-204).

References

- Agency for Toxic Substances and Disease Registry (ATSDR) (2000) Toxicological profile for arsenic. US Department of Health and Human Services, Public Health Service, Atlanta, Georgia
- Department of Health (2006) Health and national health insurance annual statistics information service. Department of Health, Ministry of Interior, Executive Yuan, Taipei, Taiwan, ROC (in Chinese)
- Department of Statistics (2006) Yearly statistics of population. Department of Statistics, Ministry of Interior, Executive Yuan, Taipei, Taiwan, ROC (in Chinese)
- Fisheries Administration (2006) Taiwan area: processed fishery products. Fisheries statistical year book. Fisheries Administration, Council of Agriculture, Executive Yuan, Taipei, Taiwan, ROC (in Chinese)
- Huang YK, Lin KH, Chen HW, Chang CC, Liu CW, Yang MH, Hsueh YM (2003) Arsenic species contents at aquaculture farm and in farmed mouthbreeder (*Oreochromis mossambicus*) in blackfoot disease hyperendemic areas. Food Chem Toxicol 41:1491–1500. doi:10.1016/S0278-6915(03)00165-0
- Lawrence GS, Gobas FAPC (1997) A pharmacokinetic analysis of interspecies extrapolation in dioxin risk assessment. Chemosphere 35:427–452. doi:10.1016/S0045-6535(97)00108-2
- Leggett RW, Williams LR, Melo DR, Lipsztein JL (2003) A physiologically based biokinetic model for cesium in the human body. Sci Total Environ 317:235–255. doi:10.1016/S0048-9697(03)00333-4
- Ling MP, Liao CM, Tsai JW (2005) A PBTK/TD modeling-based approach can assess arsenic bioaccumulation in farmed tilapia *Oreochromis mossambicus* and human health risks. Integr Environ Assess Manage 1:40–45. doi:10.1897/IEAM_2004a-004.1
- Lung SCC, Chen CF, Hu SC, Bau YP (2003) Exposure of Taiwan residents to polychlorinated biphenyl congeners from farmed, ocean-caught, and imported fish. Environ Sci Technol 37:4579–4585. doi:10.1021/es026478f
- Mann S, Droz PO, Vahter M (1996) A physiologically based pharmacokinetic model for arsenic exposure. II. Validation and application in humans. Toxicol Appl Pharmacol 140:471–486. doi:10.1006/taap.1996.0244
- Tseng CH, Chong CK, Tseng CP, Centeno JA (2007) Blackfoot disease in Taiwan: its link with inorganic arsenic exposure from drinking water. Ambio 36:82–84. doi:10.1579/0044-7447(2007)36[82:BDITIL]2.0.CO;2
- US Environmental Protection Agency (USEPA) (1998) Guidelines for ecological risk assessment. EPA/630/R/95/002F. USEPA, Washington, DC
- US Environmental Protection Agency (USEPA) (2000) Guidelines for assessing chemical contaminant data for use in fish advisories. II. Risk assessment and fish consumption limits. EPA/823/B/00/008. USEPA, Washington, DC
- Yu D (1998) Uncertainties in a pharmacokinetic modeling for inorganic arsenic. J Environ Sci Health A33:1369–1390. doi:10.1080/10934529809376794
- Yu D (1999a) A physiologically based pharmacokinetic model of inorganic arsenic. Regul Toxicol Pharmacol 29:128–141. doi:10.1006/rtph.1999.1282
- Yu D (1999b) A physiologically modeling of inorganic arsenic: a short-term oral exposure model for humans. Chemosphere 39:2737–2747. doi:10.1016/S0045-6535(99)00207-6
- Yu WH, Harvey CM, Harvey CF (2003) Arsenic in groundwater in Bangladesh: a geostatistical and epidemiological framework for evaluating health effects and potential remedies. Water Resour Res 39:1146. doi:10.1029/2002WR001327