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ScienceDirect
Ecotoxicology and Environmental Safety 70 (2008) 27–37
Ecotoxicology and Environmental Safety
www.elsevier.com/locate/ecoenv

Highlighted article

Arsenic cancer risk posed to human health from tilapia consumption in Taiwan

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Received 8 May 2007; received in revised form 4 October 2007; accepted 20 October 2007
Available online 18 December 2007

Abstract

Ingested inorganic arsenic is strongly associated with a wide spectrum of adverse health outcomes. We propose a bioaccumulation and the Weibull model-based epidemiological framework to accurately estimate the reference arsenic intake guideline for tilapia consumption and tilapia-cultured water arsenic concentration based on bioaccumulations of tilapia and gender/age/cancer-specific epidemiological data from the arseniasis-endemic area in Taiwan. Our results show a positive relationship between arsenic exposure and age/gender- and cancer-specific cumulative incidence ratio using Weibull dose–response model. Based on male bladder cancer with an excess lifetime cancer risk of 10^{-4}, we estimate the reference tilapia inorganic arsenic guideline value to be $0.084\,\mu g\,g^{-1}$ dry wt based on the suggested daily consumption rate of $120\,g\,d^{-1}$. Our findings show that consumption of tilapia in a blackfoot disease (BFD)-endemic area poses no significant cancer risk (excess cancer risks ranging from 3.4×10^{-5} to 9.3×10^{-5}), implying that people in BFD-endemic areas 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 integrating the bioaccumulation concept and epidemiological investigation of humans exposed to arsenic, we can provide a scientific basis for risk analysis to enhance risk management strategies.

Keywords: Arsenic; Human health; Epidemiology; Bioaccumulation; Tilapia; Cancer; Risk; Blackfoot disease

1. Introduction

Previous epidemiological studies have indicated that ingested inorganic arsenic is strongly associated with a wide spectrum of adverse health outcomes, primary cancers (lung, bladder, kidney, skin) and other chronic diseases such as dermal, cardiovascular, neurological, and diabetic effects in an arseniasis-endemic area in southwestern and northeastern Taiwan (Chen et al., 2001a, b; Smith et al., 2002; Chiou et al., 2005, 2001; Chen et al., 2005; Yang et al., 2005, 2003a, b). Chronic and systemic exposure to arsenic is known to lead to serious disorders, such as vascular diseases (Blackfoot disease (BFD) and hypertension) and irritations of the skin and mucous membranes, as well as dermatitis, keratosis, and melanosis. The clinical manifestations of chronic arsenic intoxication are referred to as arsenicosis (hyperpigmentation and keratosis). There is, however, no effective therapy for arsenicosis. Potential treatment involves reducing arsenic exposure and providing specific drugs for recovery and/or preventing disease progression.

Drinking water and food are the two major sources of arsenic exposure. Toxicity of an exposure is dependent on the chemical form(s) of arsenic. This has caused an increase in speciation-based analyses (Schoof et al., 1999), especially in dietary samples containing a mixture of arsenicals. Chronic toxicity is observed from exposure to drinking

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0147-6513/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.ecoenv.2007.10.018

water that contains ppb levels of inorganic arsenic (NRC, 2001). Higher doses of arsenic are acutely toxic (LD50, mice nearly 10 mg sodium arsenite kg^{-1}) (Hughes, 2002). On the basis of this, the World Health Organization (WHO) has set a tolerable daily intake for arsenic of 0.15 mg d^{-1} for a 70 kg person (WHO, 1989). The final regulation by the US Environmental Protection Agency (USEPA) on arsenic in drinking water lowered the standard from 50 to 10 μg L^{-1} (USEPA, 2002). There are still great uncertainties on the health effects of arsenic at low doses. Research is needed to investigate and assess human health effects of arsenic at low concentrations using biologically based mechanistic models.

Tilapia (*Oreochromis mossambicus*), a traditional food fish for people in Taiwan, is appreciated for its delicacy and is the second most important farmed fish in Taiwan. Currently, tilapia production is nearly 84,000 ton yr^{-1} (6.3% of total fisheries production) in that 84% tilapia production was produced from the southwestern coastal area (http://www.fagov.tw/chn/statistics_price/year_book/2005c/94tab8_6.pdf; http://www.fagov.tw/chn/statistics_price/year_book/2005c/94tab8_3.pdf). Farming of tilapia is therefore a promising business. Most tilapia farms are located at the southwestern coastal area of Taiwan, where the inhabitants used to suffer from BFD due to long-term exposure to inorganic arsenic in groundwater (Chen et al., 1988, 2001a). Currently, people living in BFD-endemic areas do not drink water from groundwater because tap water has been made available in these areas. Groundwater, however, is still utilized for aquaculture purposes (Liu et al., 2006). Increasing evidence both from field observation and experimental studies shows that a significant correlation exists between tilapia arsenic burden and cultured water arsenic contents in BFD-endemic areas (Huang et al., 2003a, b; Liao et al., 2003, 2004,; Tsai and Liao, 2006; Jang et al., 2006). If farmed tilapia is not contaminated by arsenic, it is a health food with valuable nutrients such as omega-3 polyunsaturated fatty and muscle proteins, which are well known to have certain benefits to human health (Huang et al., 2004; Tokur et al., 2004).

The bioconcentration factor (BCF) is generally adopted to estimate the propensity of an organism accumulating chemicals. Fish are targets for BCF assessments because of their importance as a human food source and the availability of standardized testing protocols. Measured or predicted BCFs are a requisite component for both environmental and human risk assessment (Liao and Ling, 2003; Jang et al., 2006). Great potential benefits could be gained from appropriately employing arsenic bioaccumulation of tilapia to estimate site-specific equilibrium BCF values for evaluating the reference cultured water arsenic guideline.

The analysis in this paper is based on a variety of survey data and prior analyses. We estimate the incidence ratios of various types of internal cancers. The epidemiological survey provided by the Blackfoot Disease Study Group (BDSG) in Taiwan (cjchen@ha.mc.ntu.edu.tw) enables us to estimate the dose–response function for arsenic-induced cancers. This paper is the first to report dose–response for internal cancers in BFD-endemic areas based on a recent survey on arsenic epidemiology. The choice of an appropriate dose–response model to represent pharmacodynamic characteristics is an important consideration in risk assessment. There are three empirical dose–response models that have received some attentions. The log-logistic model uses the log-logistic distribution as a tolerance distribution. The log-probit model uses the lognormal as a tolerance distribution. The Weibull model uses the Weibull distribution. At high doses, all three models are quite similar. At low doses, however, the log-logit and Weibull models are linear on a log–log scale, whereas the log-probit model has a substantial curvature and gives a much lower risk estimate. Christensen and Nyholm (1984), ten Berge (1999), and Kodell et al. (2006) suggested that the Weibull model was particularly well suited for a long-term low-dose exposure purpose on dose–response modeling on lifetime cancer risk estimation.

We argue that, by understanding the linkages between bioaccumulation 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. The purposes of this study are twofold: (1) to estimate the reference tilapia-cultured water arsenic guideline based on the proposed bioaccumulation and epidemiological framework on the basis of gender- and age-specific epidemiological data on arsenic exposure, cancer incidences, and at-risk population obtained from studies conducted in arseniasis-endemic areas and (2) to quantify the internal cancer risks of arsenic exposure from farmed tilapia consumption in BFD-endemic areas.

2. Materials and methods

Our risk assessment approach (Fig. 1) was proposed based on a risk analysis approach for estimating the reference cultured water arsenic guidelines and excess lifetime cancer risk estimates in that the methodology can be divided into 4 phases: (A) problem formulation, (B) exposure analysis, (C) effect analysis, and (D) risk characterization. The four phases were based on the USEPA ecological risk assessment paradigm (USEPA, 1998) to account for the human–arsenic–tilapia system response to a spectrum of adverse health effects that have been identified across a range of gender/age- and site-specific scales and are described in subsequent sections.

2.1. Quantitative tilapia arsenic data

We re-analyze quantitatively the valuable data obtained from Huang et al. (2003b) regarding arsenic species contents in aquaculture pond water and farmed tilapia based on a field survey in 4 major townships of Putai, Yichu, Peimen, and Hsuehchia in BFD-endemic areas to reconstruct our tilapia arsenic data (Table 1). Table 1 indicates that the average total arsenic concentration in tilapia-cultured water was 48.93 μg L^{-1} and the percentages of inorganic arsenic in total arsenic ranged from 70% to 89%, whereas the average tilapia total arsenic level was 0.858 μg g^{-1} dry wt. The provision of aquaculture water arsenic standard is recommended as 50 μg L^{-1} by the Taiwan regulatory authority (EPAROC, 1998;

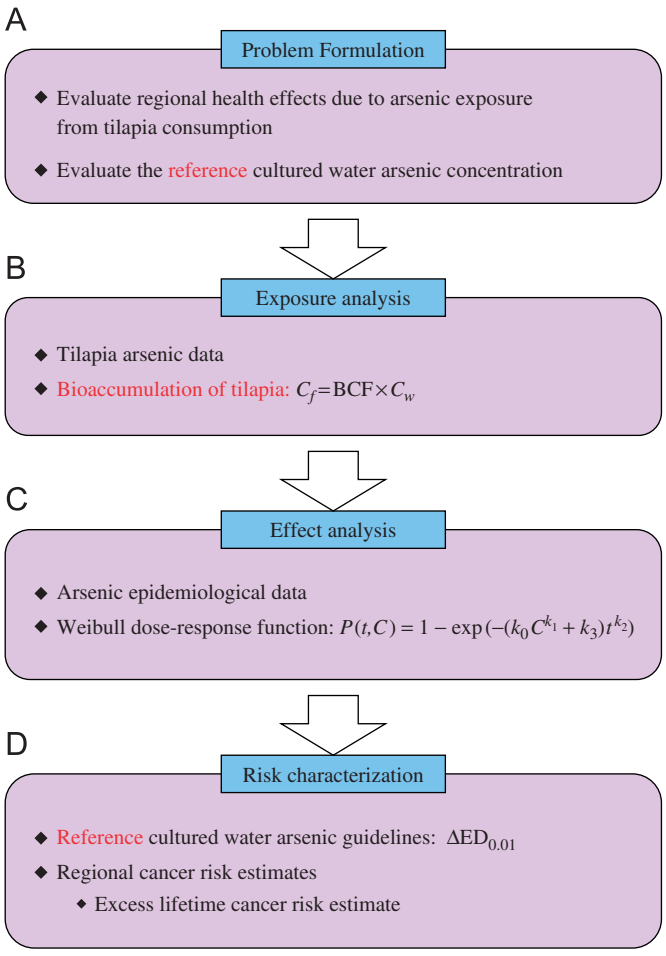

Fig. 1. Schematic diagram showing the proposed risk analysis approach for estimating the reference cultured water arsenic guidelines and excess lifetime cancer risk estimates. Modified from USEPA (1998).

http://w3.epa.gov.tw/epalaw/index.aspx). Han et al. (1998) provided data for farmed fish consumption rates for adults, indicating that the fish consumption rates ranged from 10 to 30 g d^{-1} (% of respondents was 50%) and 35 to 70 g d^{-1} (% of respondents was 18%) for 2–6 and 7–14 meals per week, respectively, based on a brief questionnaire for seafood consumption frequency and weeks of consumption for 850 residents in Taiwan Region.

2.2. Quantitative arsenic epidemiological data

A remarkable data set related to arsenic epidemiology of gender-specific and age-adjusted internal cancer incidences including liver, lung, and bladder cancers in arseniasis-endemic areas in Taiwan provided by the BDSG gives us the opportunity to test all theoretical considerations of arsenic exposure effects and quantify its strength. We appraise the data set from the cohort studies in arseniasis-endemic areas in Taiwan to quantitatively reconstruct pooled arsenic epidemiological data of gender- and cancer-specific cumulative incidence ratios (Fig. 2). BDSG used a standardized questionnaire interview to collect information including arsenic exposure, cigarette smoking and alcohol consumption, and other risk factors such as sociodemographic characteristics, residential and occupational history, and history of drinking well water by 2 well-trained public health nurses. A total of 2050 residents in 4 townships of Peimen, Hsuehchia, Putai, and Yichu on the southwestern coast and 8088 in 4 townships of Tungshan, Chuangwei, Chiaohsi, and Wuchieh in the northeastern Lanyang Plain were followed up for an average period of 8 years (Chen et al., 2004). A detailed description of the recruitment procedure for cohort studies and cancer cases ascertainment has been reported previously (Chen et al., 2004; Chiou et al., 2005).

Residents in the southwestern endemic area had consumed artesian well water (100–300 m in depth) for more than 50 years before the implementation of the tap water supply system in the early 1960s. The estimated amount of ingested arsenic mainly from drinking water was $\geqslant$1 mg d^{-1} in this area. Residences in the northeastern endemic area had consumed water from shallow well (<40 m in depth) since the late 1940s through the early 1990s, when the tap water system was implemented. Arsenic levels in well water in the northeastern Lanyang Plain ranged from <0.15 to >3000 μg L^{-1} (Chen et al., 2004). The larger number of study participants (10,138 residents from southwestern and northeastern Taiwan), longer period of follow-up with more incident cancer cases, and wider range of arsenic exposure levels gives us with a unique opportunity to further investigate the dose–response relationship between ingested arsenic exposure and cancer risks.

2.3. Weibull dose–response function and bioaccumulation of tilapia

Here we use the Weibull probability density function to account for the age-specific incidence ratio for human long-term exposure to low doses of arsenic:

$$g(t, \varepsilon(C)) = \varepsilon(C) k_2 t^{k_2 - 1} \exp(-\varepsilon(C) t^{k_2}), \quad (1)$$

with

$$\varepsilon(C) = k_0 C^{k_1} + k_3, \quad (2)$$

where $g(t,\varepsilon(C))$ represents the cancer-specific incidence ratio for humans exposed to arsenic concentration C (μg L^{-1}) at age t (yr), $\varepsilon(C)$ is the C-dependent shape parameter, and k_0, k_1, k_2, and k_3 are the cancer-specific best-fitted parameters. The cumulative incidence ratio for human exposed to arsenic concentration C at age t can then be obtained by the integral of Eq. (1) as

$$P(t, C) = \int_0^t g(t, \varepsilon(C))\, dt = 1 - \exp(-\varepsilon(C) t^{k_2}) = 1 - \exp(-(k_0 C^{k_1} + k_3) t^{k_2}). \quad (3)$$

We employed TableCurve 3D (Version 4, AISN Software Inc., Mapleton, OR, USA) to perform model fitting to pooled arsenic epidemiological data from BDF-endemic areas and Lanyang Plain to reflect the reasonable trend of dose–response relationship (Fig. 2).

We used a bioaccumulation model to describe the arsenic concentration in tilapia exposed to arsenic in an aquaculture pond. For a long-term arsenic exposure for tilapia, the whole body burden (muscle) of arsenic in tilapia can be expressed as

$$C_f = \frac{k_1}{k_2} C_w = \mathrm{BCF} \times C_w, \quad (4)$$

where C_f is the arsenic concentration in tilapia (μg g^{-1} dry wet), C_w is the dissolved arsenic concentration in water (mg L^{-1}), k_1 is the uptake rate constant (mL g^{-1} g^{-1}) and k_2 is the depuration rate (d^{-1}) constant of arsenic, and BCF = $k_1/k_2 = C_f/C_w$ is the equilibrium bioconcentration factor (BCF) for tilapia (mL g^{-1}) that can be estimated from tilapia arsenic data in Table 1.

2.4. Quantitative arsenic intake and risk estimates

We incorporated fish consumption rate distribution based on Han et al. (1998) into a Weibull dose–response function to evaluate the excess lifetime cancer risks (Fig. 1C). We evaluate the reference tilapia-cultured water guideline based on the human health effects. We link drinking water inorganic arsenic estimates with the average tilapia inorganic arsenic body burden (the average BCF value) associated with a conservative daily fish consumption rate of 120 g d^{-1} recommended by the Department of Health, ROC to estimate the reference tilapia-cultured water arsenic guideline value (Fig. 1D). Table 1 indicates that the average percentage of inorganic arsenic in total arsenic is 81%. Chen et al. (1995) also indicated

Table 1
Arsenic species contents in tilapia-cultured water and farmed tilapia (*Oreochromis mossambicus*) in the BFD-endemic area[a]

Arsenic species	Putai ($n=5$)[b]	Yichu ($n=7$)	Peimen ($n=2$)	Hsuehchia ($n=7$)	Average ($n=21$)
Arsenic species in cultured water ($\mu g\,L^{-1}$)					
As(III)	0.2[c] (0.1)	0.5 (0.4)	ND[d]	0.01 (0.01)	0.2 (0.1)
As(V)	66.9 (32.6)	10.2 (2.4)	172.6 (118.5)	11.1 (3.5)	39.5 (15.5)
MMA[e]	0.06 (0.05)	0.3 (0.2)	0.2 (0.2)	0.04 (0.04)	0.15 (0.06)
DMA[f]	0.3 (0.2)	0.7 (0.3)	5.4 (3.5)	ND	0.8 (0.4)
Total As	75.8 (38.8)	15.1 (2.9)	221.0 (138.8)	14.4 (4.1)	48.93 (18.4)
InAs/total As (%)	88.5	70.1	78.1	77.2	81.1
Arsenic species in tilapia ($\mu g\,g^{-1}\,dry\,wt \times 10^{-2}$)					
	($n=16$)	($n=21$)	($n=6$)	($n=25$)	($n=68$)
As(III)	4.72 (2.06)	1.71 (0.71)	3.9 (3.8)	1.86 (0.71)	2.67 (1.30)
As(V)	2.97 (0.92)	1.47 (0.7)	2.8 (1.15)	2.46 (1.2)	2.20 (0.91)
MMA	2.34 (2.04)	0.71 (0.44)	0.1 (0.1)	0.75 (0.70)	1.06 (0.88)
DMA	16.46 (7.67)	12.23 (5.19)	6.05 (0.85)	11.91 (3.43)	12.56 (4.74)
Total As	168.19 (33.52)	51.23 (9.6)	52.15 (7.3)	70.10 (9.01)	85.77 (14.81)

[a]Reanalyzed from Huang et al. (2003).
[b]Sample number.
[c]Mean (standard error).
[d]ND: non detectable.
[e]MMA = monoethylarsonic acid.
[f]DMA = dimethylarsonic acid.

that the ratios of inorganic arsenic to total arsenic in well water in southwestern coasts and Lanyang Plain were larger than 90%. Here we use 90% of inorganic arsenic in total arsenic as the evaluation basis.

We assume that daily water uptake rate and tilapia consumption rate undergo a variability analysis. To explicitly quantify the uncertainty/variability of data, a Monte Carlo simulation is performed with 10,000 iterations (stability condition) to obtain the 95% confidence interval (CI). The Monte Carlo simulation is implemented by using the Crystal Ball software (Version 2000.2, Decisioneering Inc., Denver, CO, USA). The χ^2 and Kolmogorov–Smirnov (K–S) statistics were used to optimize the goodness-of-fit of the distribution. Results show that the selected lognormal distribution had the optimal K–S and χ^2 goodness-of-fit for both drinking water uptake and tilapia consumption rates.

Morales et al. (2000) suggested that the use of 1% and 5% excess risks (ΔED_{01} and ΔED_{05}, respectively) for the point-of-departure analysis for cancer risk assessment suggested by USEPA (1996) is better than that of 10% excess risk (ΔED_{10}) because an excess risk of 10% is relatively large and happens only at relative high doses in epidemiological studies. The USEPA-suggested point-of-departure analysis for cancer risk assessment is to estimate a point on the exposure response curve within the observed range of the data and then extrapolate it linearly to a lower dose (Morales et al., 2000). Morales et al. (2000) also pointed out that the traditionally employed unit excess lifetime risk of 10^{-6} is probably unreliable for epidemiological data where exposure is not typically measured accurately enough to extrapolate to such low risk levels. In the present study, we use 0.01% excess risk ($\Delta ED_{0.01}$) and ΔED_{01} point-of-departure to quantify the risk estimates. We perform excess cancer risk assessment by the Monte Carlo simulation technique.

3. Results

3.1. Fitting Weibull model to arsenic epidemiological data

Table 2 shows the best-fitted parameters k_0, k_1, k_2, and k_3 in Eq. (3) for lung, liver, and bladder cancers for each gender by fitting a Weibull dose–response function (Eq. (3)) to gender- and cancer-specific cumulative incidence ratios (Fig. 2). Here we estimate the Weibull dose–response function for the background incidence of internal cancers and for the total incidence at a given arsenic concentration. We obtain Eq. (3) by incorporating a background dose–response function into the original dose–response function. We use a comparison population defining unexposed internal mortality rates as our background dose–response function, where the internal cancer mortality data were collected from death certificates of residents of 42 villages during 1973–1986 in Taiwan (Morales et al., 2000). Here we define $\Delta P \equiv P(t, C) - P(t, 0)$ to be the background-adjusted cumulative incidence rate of internal cancers.

Our results indicate that bladder cancer has the highest r^2 values (>0.85) for all genders than those of lung (nearly 0.6) and liver (<0.5) cancers, respectively (Table 2). For bladder cancer, r^2 values are all larger than 0.85 (male $r^2 = 0.86$ and female $r^2 = 0.87$), indicating that arsenic exposure and age are the most influential factors for bladder cancer incidence. Specifically, arsenic exposure has notable influence than that of age ($k_1 = 1.36$ and $k_2 = 0.6$) for females, whereas for males arsenic exposure and age have significant contributions to the incidence ($k_1 = k_2 = 1.13$) (Table 2). Generally, our result indicates that arsenic exposure is the major attribute to bladder cancer incidence ratio for the study participants of residents in arseniasis-endemic areas. Fig. 3A gives a model fitting for male bladder cancer ranging from 30 to 80 years, showing that the response surfaces of dose–response function associated with an age-specific relationship between cumulative incidence ratio and arsenic exposure can be fit reasonably well by the Weibull model.

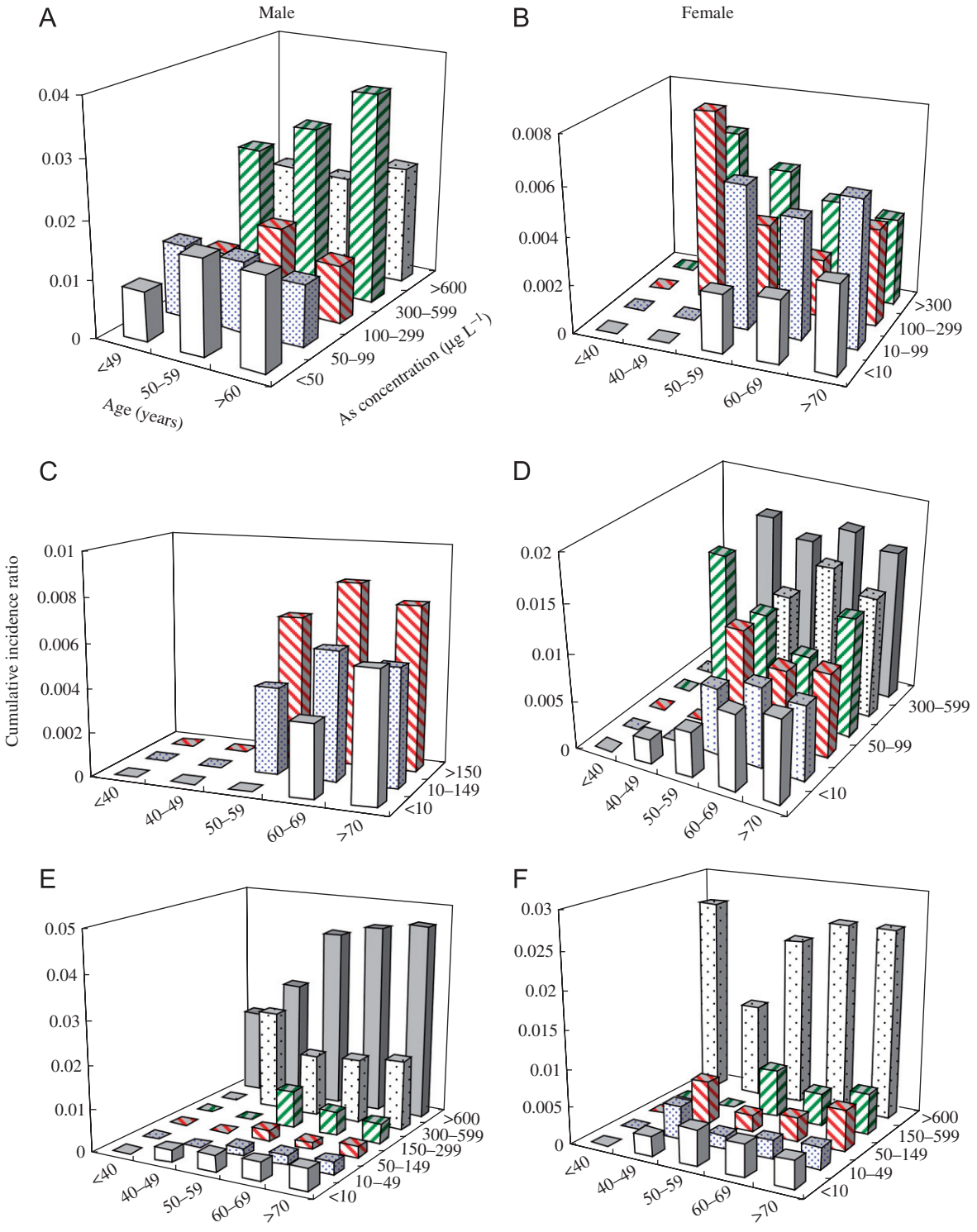

Fig. 2. Arsenic epidemiological data of gender- and cancer-specific cumulative incidence ratios in arseniasis-endemic areas in Taiwan (Chen et al., 2004; Chiou et al., 2005), showing the male/female liver cancer (A, B), lung cancer (C, D), and bladder cancer (E, F), respectively.

Therefore, based on male bladder cancer as our index cancer, we estimate the drinking water arsenic concentration based on Fig. 3A with excess risk of 10^{-4} suggested by USEPA and a median daily drinking water uptake rate of $3.29\,L\,d^{-1}$ (Fig. 3B) for a lifetime exposure duration of 75 years and an average male body weight of 60 kg. Our result shows that the water inorganic arsenic concentration is estimated to be $3.4\,\mu g\,L^{-1}$ based on a 0.01% excess risk ($\Delta ED_{0.01}$). We further use 1% excess dose (ΔED_{01}) to linearly extrapolate to the $\Delta ED_{0.01}$ point at low concentration ranges, resulting in a water inorganic arsenic concentration of $2\,\mu g\,L^{-1}$. This result indicates that Weibull dose–response function for male bladder cancer demonstrates a nearly linear with slightly concave characteristic at

Table 2
Gender- and cancer-specific best fitted parameters in Weibull dose–response function

Cancer	k_0	k_1	k_2	k_3	r^2
Male					
Lung[a]	1.07×10^{-7}[b] ($0–1.17\times10^{-6}$)[b]	0.7 (0–2.11)	1.46 (0.37–2.55)	6.25×10^{-6} ($0–3.49\times10^{-5}$)	0.67
Liver[c]	5.24×10^{-7} ($0–5.00\times10^{-6}$)	0.823 (0–2.01)	1.21 (0.33–2.09)	6.01×10^{-5} ($0–2.82\times10^{-4}$)	0.45
Bladder[c]	1.92×10^{-7} ($0–8.29\times10^{-7}$)	1.13 (0.73–1.54)	1.13 (0.66–1.61)	4.38×10^{-9} ($0–2.67\times10^{-5}$)	0.86
Female					
Lung[a]	8.72×10^{-8} ($0–9.73\times10^{-7}$)	0.83 (0–2.26)	1.45 (0.65–2.26)	1.45×10^{-5} ($0–6.40\times10^{-5}$)	0.58
Liver[c]	1.50×10^{-5} ($0–8.90\times10^{-5}$)	0.14 (0–0.43)	1.09 (0–2.2)	1.13×10^{-5} ($0–6.74\times10^{-5}$)	0.41
Bladder[c]	2.02×10^{-7} ($0–1.28\times10^{-6}$)	1.36 (0.63–2.08)	0.6 (0.04–1.16)	1.03×10^{-4} ($0–1.76\times10^{-3}$)	0.87

[a]Excluding smoking population.
[b]Best fitting value with 95% CI shown in parenthesis.
[c]A comparison population is used to define unexposed cancer mortality rates (i.e., cumulative cancer incidence ratio at $C=0$: $P(t,0)$) in that cancer mortality data were collected from death certificates of residents of 42 villages during 1973–1986 in Taiwan (Morales et al., 2000).

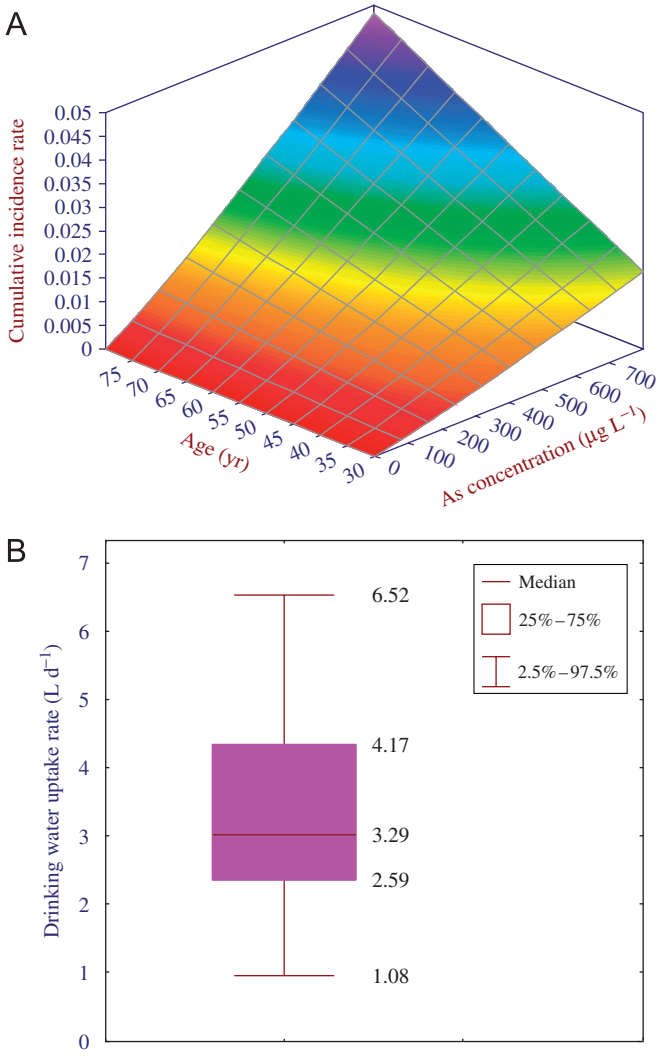

Fig. 3. (A) Best fitted Weibull model-based dose–response surfaces reflecting an age-specific relationship between cumulative incidence ratio and arsenic exposure for male bladder cancer. (B) A box and whisker plot showing the daily drinking water uptake rate distribution.

low arsenic concentration ranges. Therefore, based on male bladder cancer as the index, internal cancer with an excess lifetime risk of 10^{-4} to obtain the drinking water arsenic concentration of $3.4\,\mu g\,L^{-1}$ ($r^2>0.8$) can be reasonably adopted as a reference guideline value for drinking water in the present study.

3.2. Reference tilapia-cultured water arsenic guideline

We evaluate the reference tilapia-cultured water inorganic arsenic guideline value based on the average inorganic arsenic (As(III)+As(V)) concentration of $39.7\,\mu g\,L^{-1}$ in tilapia-cultured water with an average $0.0497\,\mu g\,g^{-1}$ dry wt of inorganic arsenic in tilapia in BFD-endemic areas (Table 3). Here we adopt the water arsenic concentration of $3.4\,\mu g\,L^{-1}$ with a median daily drinking water uptake rate of $3.29\,L\,d^{-1}$ to derive the reference tilapia-cultured water arsenic guideline value (Table 3): (1) Daily maximum arsenic ingestion rate: $D=3.29\,L\,d^{-1}\times3.4\,\mu g\,L^{-1}\times0.9=10.1\,\mu g\,d^{-1}$ based on 90% of inorganic arsenic content in total organic. (2) Inorganic arsenic level in tilapia: $C_{f,s}=10.1\,\mu g\,d^{-1}/120\,g\,d^{-1}=0.084\,\mu g\,g^{-1}$ dry wt based on the suggested daily fish consumption of $120\,g\,d^{-1}$ by the Department of Health, ROC. (3) Cultured water arsenic concentration: $C_{w,s}=C_{f,s}/BCF_{avg}=(0.084\,\mu g\,g^{-1}\,dry\,wt)/(1.25\times10^{-3}\,L\,g^{-1})=67.09\,\mu g\,L^{-1}$ based on an average $BCF_{avg}=1.25\times10^{-3}\,L\,g^{-1}$ (Table 3). Furthermore, the site-specific reference cultured water arsenic guidelines are also estimated to be 73, 28, 216, and $21\,\mu g\,L^{-1}$, respectively, for Putai, Yichu, Peimen, and Hsuehchia, based on the site-specific BCF values.

3.3. Regional cancer risk estimates

We evaluate the excess cancer risk estimates based on the Weibull dose–response function for male bladder cancer as

Table 3
Recommended reference inorganic arsenic guideline in tilapia-cultured water in BFD-endemic area

As species	Putai ($n=5$)[a]	Yichu ($n=7$)	Peimen ($n=2$)	Hsuehchia ($n=7$)	Average ($n=21$)
Mean arsenic species in cultured water (C_w, $\mu g\,L^{-1}$)					
As(III)	0.2	0.5	ND	0.01	0.2
As(V)	66.9	10.2	172.6	11.1	39.5
As(III) + As(V)	67.1	10.7	172.6	11.11	39.7
Mean arsenic species in tilapia (C_f, $\mu g\,g^{-1}\,dw \times 10^{-2}$)					
As(III)	4.72	1.71	3.9	1.86	2.67
As(V)	2.97	1.47	2.8	2.46	2.30
As(III) + As(V)	7.69	3.19	6.7	4.32	4.97
$BCF = C_f/C_w$ ($mL\,g^{-1}$)					
	1.14	2.98	0.39	3.89	1.25
Reference cultured water inorganic arsenic concentration ($\mu g\,L^{-1}$)					
	73.32	28.21	216.39	21.60	67.09

[a] n is the sampling number.

our index internal cancer ($r^2>0.85$ and $k_1=k_2$ (Table 2)). We incorporate farmed fish consumption rate frequencies (Han et al., 1998) and tilapia inorganic arsenic burden data (Table 1) into the Weibull dose–response function for male bladder cancer to assess the excess lifetime cancer risks in BFD-endemic area (Fig. 4). Fig. 4 shows that the excess cancer risk estimates (ranging from 3.4×10^{-5} to 9.3×10^{-5}) are all within the acceptable value of 10^{-4} in that Putai and Hsuehcuia have the highest bladder cancer risk (99%) of 9.3×10^{-5} and 6.7×10^{-5}, respectively (Figs. 4B and E). The 90% risks are 4.2×10^{-5}, 3.6×10^{-5}, 1.7×10^{-5}, and 2.0×10^{-5} for Putai, Peiman, Yichu, and Hsuehcuia, respectively (Figs. 4B–E). Our result indicates that human exposure to the consumption of tilapia in BFD-endemic areas may pose no significant cancer risks. The result also implicates that people in BFD-endemic area are not readily associated with higher fatalities for bladder cancer exposed from tilapia consumption.

4. Discussion

4.1. Implications of the reference arsenic guideline

To date, the total arsenic standard for aquaculture water is recommended to be $50\,\mu g\,L^{-1}$ by Taiwan regulatory authorities. Huang et al. (2003b) indicated that the average ratio of inorganic arsenic to total arsenic of cultured water is 81.1%, with a min–max from 70.1% to 88.5% in southwestern coastal areas, resulting in the reference inorganic arsenic guideline for cultured water to be calculated as $50\,\mu g\,L^{-1}\times81.1\%=41\,\mu g\,L^{-1}$, with a min–-max from 35 to $44\,\mu g\,L^{-1}$. Hence, the reference guideline of $67.09\,\mu g\,L^{-1}$ is acceptable.

According to the recommended reference inorganic arsenic guideline in Table 3, the inorganic arsenic in cultured water in Putai is the second high concentration ($67.1\,\mu g\,L^{-1}$ less than $172.6\,\mu g\,L^{-1}$ in Peimen); however, the highest excess risk of framed tilapia consumption also occurred in Putai (maximum 9.3×10^{-5} with 90% less than 4.2×10^{-5}) in Fig. 4. The reason may be that the inorganic arsenic level in tilapia is highest than those of others ($C_f=7.69\,\mu g\,g^{-1}$ dry wt in Table 3). Cultured water arsenic concentration is not the only determinant to affect the excess risk values. Other environmental factors such as characteristics of water chemistry and bioavailability may also affect the estimation of excess risk values. Therefore, the inorganic arsenic level in tilapia is the most direct uptake exposure concentration to human health and that may be the critical point to estimate the excess risk values.

Our study suggests that the reference cultured water arsenic guidelines are estimated to be $67.09\,\mu g\,L^{-1}$ based on the average BCF_{avg}. Furthermore, the site-specific reference cultured water arsenic guidelines are estimated to be 73, 28, 216, and $21\,\mu g\,L^{-1}$ based on the site-specific BCF values for Putai, Yichu, Peimen, and Hsuehchia, respectively. Large differences are observed on estimation of the reference cultured water arsenic guidelines based on BCF_{avg} or site-specific BCF values. On the aspect of human health, we suggest that the site-specific BCF values will be more appropriate to regulate hazard risk. From the aspect of regulatory authorities, however, a universal reference guideline may provide an effective management. Thus, our estimated reference tilapia inorganic arsenic guideline of $0.084\,\mu g\,g^{-1}$ dry wt is more appropriate than the reference cultured inorganic arsenic guideline.

Our results suggest that both BCF values of commercially important farmed species and human consumption frequencies have to be taken into account to further select appropriately the suitable farmed species with average arsenic BCF values to detail more accurately and robustly while assessing the reference cultured water arsenic guideline value on the whole. To precisely determine the risk/benefit ratios from consumption of farmed fish is complicated; cautious interpretation of present data may substantially prompt risk management strategy. We argue that the present reference water arsenic guideline value is

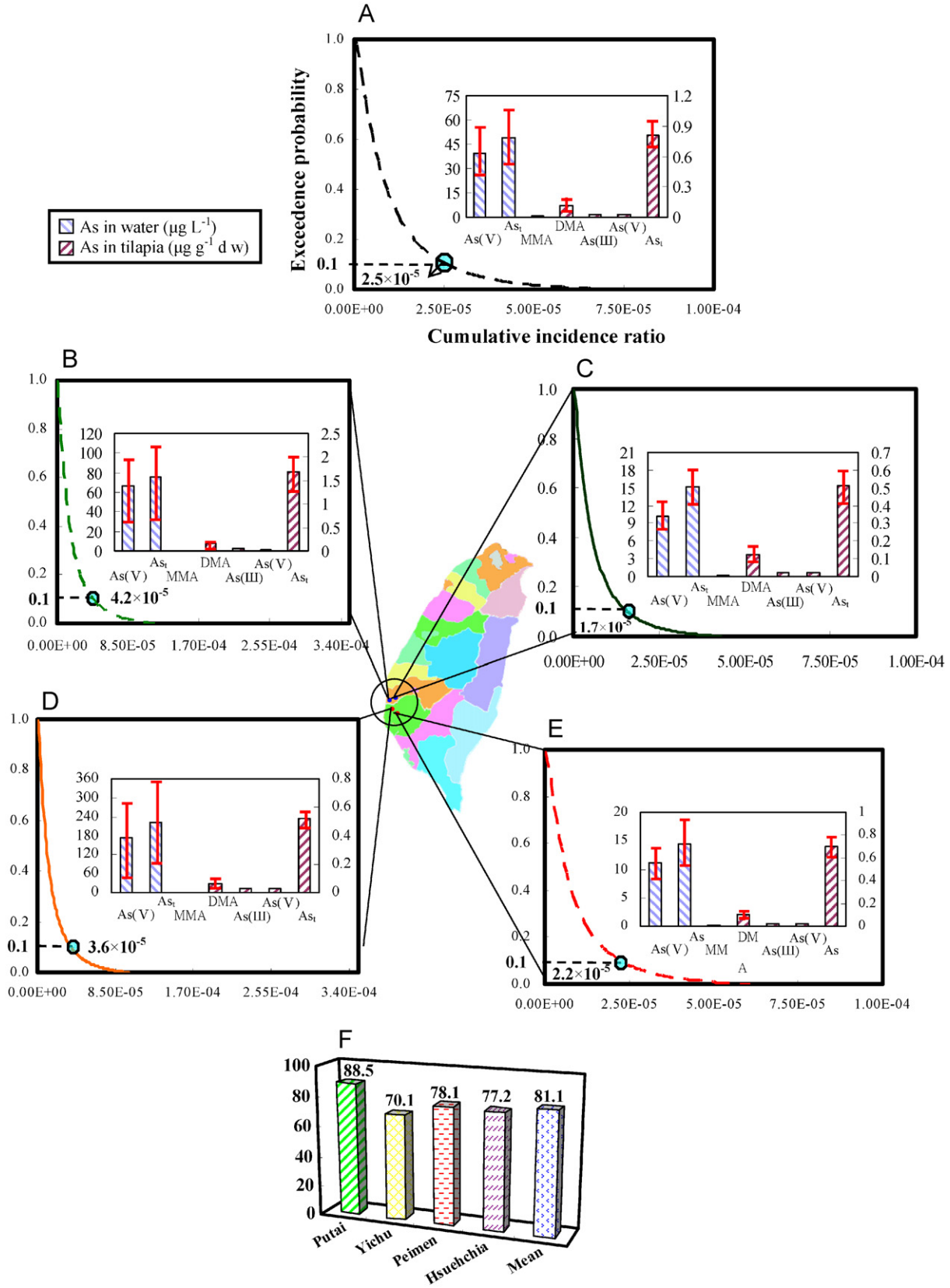

Fig. 4. Excess lifetime risk estimates of tilapia culture water and farmed tilapia based on Huang et al. (2003b) in (A) the overall BFD-endemic area, (B) Putai, (C) Yichu, (D) Peimen, and (E) Hsuehcuia. Ratios of inorganic arsenic/total arsenic in 4 major townships in the BFD-endemic area are shown in (F). Error bar indicates the standard deviation from mean.

estimated based on arsenic epidemiology data from long-term low-dose exposures and not based on animal models considering uncertainty factors used to account for potential interspecies variation in response sensitivity and potential intraspecies variation in human sensitivity.

There are a number of areas in which further research could strengthen the water arsenic reference guideline establishment (Hrudey et al., 2006). First, there is a need to conduct a more extensive characterization of the distribution of exposures within given aquaculture species population. It would be useful to characterize better the detailed information on aquaculture species arsenic data, arsenic levels in fish target organs, and site- and species-specific BCF value. Second, there is a need for sensitivity analysis using the Monte Carlo simulation model with the more detailed data sets as inputs. Relationships between the input ranges and model output should then be assessed with stepwise regression in order to identify the relationship between output variability and input uncertainties and variabilities. Finally, on the basis of the results of the sensitivity analysis, research should be directed to those parameters that, if better characterized, could most effectively reduce variability in the results.

4.2. Implications on risk management

An analysis of the implications of arsenic-induced cancer risks in arseniasis-endemic areas would be more complex and would include consideration of impacts on farmed fish production, and regionally specific information on social, demographic, and economic trends. Moreover, the arsenic-induced cancer risks may occur concurrent with human-induced changes. These human-driven transitions in arseniasis-endemic areas (e.g., cigarette smoking) are likely to have a larger impact on risk profiling than arsenic-only-induced transitions (Chen et al., 2004). Although our information may not be able to provide an unambiguous definition of cultured water arsenic and risk estimates of tilapia consumption, it may help to inform public and regulatory authorities on discussions of risk management and communication by drawing attention to the worldwide arsenic issues.

Scientific progress in human and environmental risk management for assuring safe arsenic intake clearly depends on interdisciplinary collaboration. This task requires defining environmental risk assessment protocols appropriate for the specific social and environmental conditions encountered in arseniasis-endemic areas (e.g., demographic and epidemiological history and biogeochemical and geographic information) (Nieuwenhuijsen et al., 2006). There is also a need on the part of regulatory authorities to enforce more strictly. Epidemiologists must provide the valuable yet realistic cohort studies to directly and indirectly identify certain epidemiology data to further construct the dose–response relationships as the framework for environmental management (Chappell et al., 2003). It is in this way that the epidemiologists use an understanding of the biology of diseases and the principles of epidemiology to design and conduct studies that will ultimately aid in the risk management (Chen et al., 2005). Chemists and biologists must work together to harness the potential of new screening techniques for assessing the environmental impact of arsenic, whereas environmental chemists and engineers must strive to develop more powerful strategies to mitigate arsenic-contaminated drinking water because meeting the WHO guideline of $10\,\mu g\,L^{-1}$ of arsenic is a major drinking water challenge worldwide for both geochemists and process engineers (Berg et al., 2001; Hug et al., 2001; Su and Puls, 2001). Fig. 5 summarizes our conceptual bioaccumulation and epidemiological framework, providing an accurate risk analysis for reference arsenic intake guideline estimations and implicating the interplay among system approach, regulatory requirements, and risk management. This can be grouped into three major components: (i) human health-based reference water arsenic guideline estimate based on Weibull dose–response model-based epidemiological data (Fig. 5A), (ii) reference cultured water arsenic guideline estimated by site-specific BCF values and the farmed fish consumption frequency survey (Fig. 5B), and (iii) risk management analyses and strategies to meet the human health-based arsenic intake regulations (Fig. 5C).

We recognize limitations in each of our data sources, particularly the inherent problem of uncertainty and variability of the data. The strength of these results rests on the consistent agreement of mathematical models and public and regulatory authorities' reference guideline values. Our analysis may provide a wider context for the interpretation of regional arsenic-induced cancer risk profiling that produced diverging and controversial outcomes, which have economic and policy implications. Although more complex models may be necessary to answer specific questions regarding risk or particular management strategies, our simple model captures the essential risk analysis methodology, and it is flexible enough to integrate the effects occurring at varying subpopulation scales. Our results suggest that even simple models can provide useful insights into complex bioaccumulation and epidemiological interactions in human and ecological risk management.

In conclusion, our proposed bioaccumulation and Weibull model-based epidemiological framework provide a template for integrating the tilapia arsenic data, bioaccumulation of tilapia, epidemiological data, and risk profiling techniques to accurately estimate the reference cultured water arsenic guideline associated with human arsenic intake. Our data highlight that the tilapia-cultured water inorganic arsenic concentration is estimated to be $67.09\,\mu g\,L^{-1}$ based on male bladder cancer with an excess lifetime cancer risk of 10^{-4}. Our findings further point out that consumption of tilapia in BFD-endemic areas is unlikely to pose substantial cancer risk (excess cancer risks ranging from 3.4×10^{-5} to $9.3\times10^{-5}<10^{-4}$) to public health given the most prevalent exposure routes. We are confident that our model can be easily adapted for other

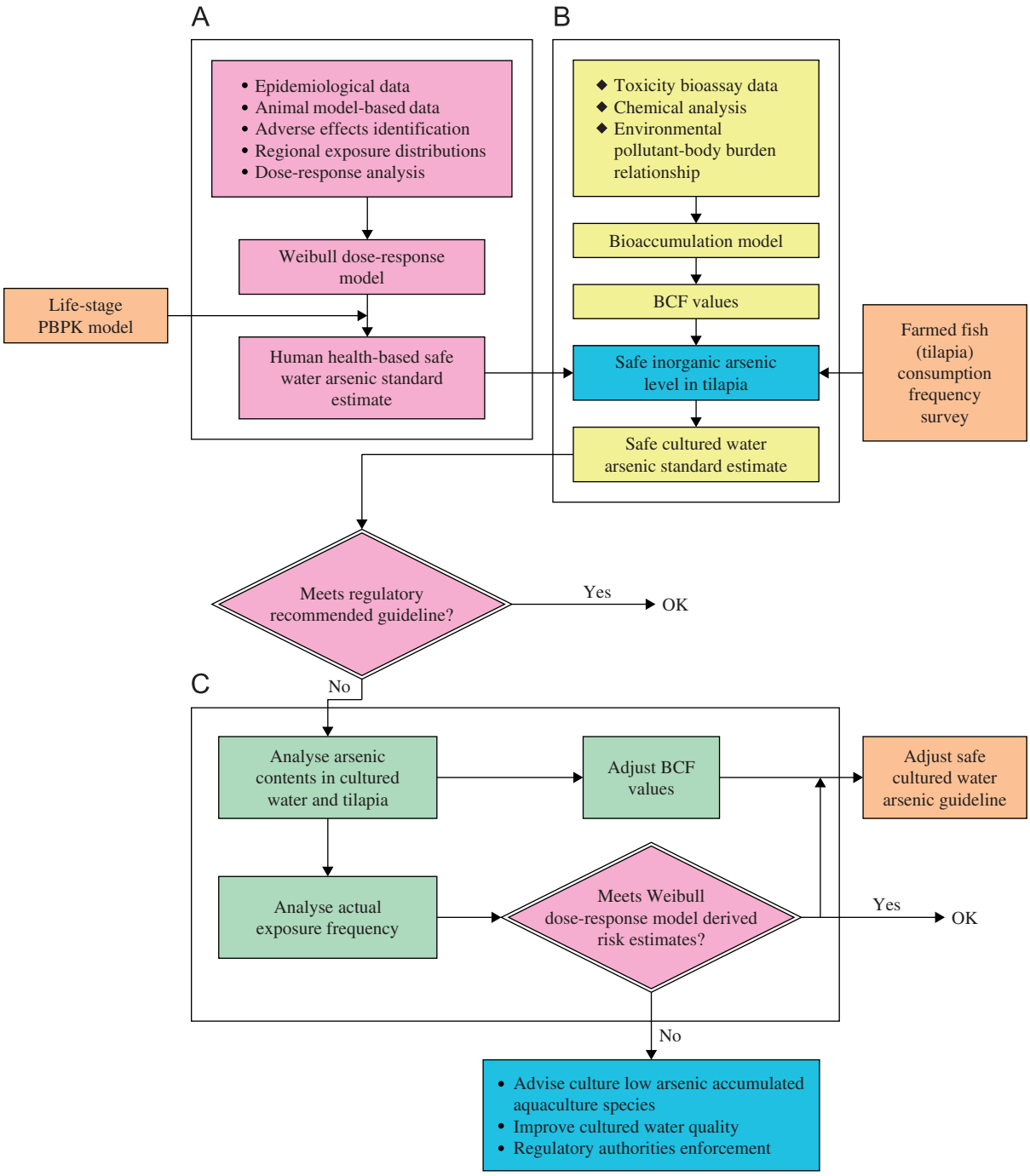

Fig. 5. A conceptual diagram showing the proposed bioaccumulation and epidemiological framework.

aquaculture species, and encourage risk managers to use the model to evaluate the potential population-level long-term low-dose cancer risk exposed to environmental micropollutants in order to recommend the appropriate reference cultured water guidelines or to quantify rigorous health risk estimates for food consumption.

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