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Assessment of Human Health Risks for Arsenic Bioaccumulation in Tilapia (*Oreochromis mossambicus*) and Large-Scale Mullet (*Liza macrolepis*) from Blackfoot Disease Area in Taiwan

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Abstract. This paper carries out probabilistic risk analysis methods to quantify arsenic (As) bioaccumulation in cultured fish of tilapia (*Orechromis mossambicus*) and large-scale mullet (*Liza macrolepis*) at blackfoot disease (BFD) area in Taiwan and to assess the range of exposures for the people who eat the contaminated fish. The models implemented include a probabilistic bioaccumulation model to account for As accumulation in fish and a human health exposure and risk model that accounts for hazard quotient and lifetime risk for humans consuming contaminated fish. Results demonstrate that the ninety-fifth percentile of hazard quotient for inorganic As ranged from 0.77–2.35 for Taipei city residents with fish consumption rates of 10–70 g/d, whereas it ranged 1.86–6.09 for subsistence fishers in the BFD area with 48–143 g/d, consumption rates. The highest ninety-fifth percentile of potential health risk for inorganic As ranged from 1.92×10^{-4}–5.25×10^{-4} for Taipei city residents eating tilapia harvested from Hsuehchia fish farms, with consumption rates of 10–70 g/d, whereas for subsistence fishers it was 7.36×10^{-4}–1.12×10^{-3} with 48–143 g/d consumption rates. These findings indicate that As exposure poses risks to residents and subsistence fishers, yet these results occur under highly conservative conditions. We calculate the maximum allowable inorganic As residues associated to a standard unit risk, resulting in the maximum target residues, are 0.0019–0.0175 and 0.0023–0.0053 μg/g dry weight for tilapia and large-scale mullet, respectively, with consumption rates of 70–10 g/d, or 0.0009–0.0029 and 0.0011–0.0013 μg/g dry weight for consumption rates of 169−48 g/d.

Arsenic (As) is widespread in the environment as a consequence of both anthropogenic and natural processes. It is a ubiquitous but potentially toxic trace element. Inorganic as well as organic forms of As are present in the environment, and the former seems to be more toxic and slightly more accumulated in some freshwater aquatic species than the latter (Spehar *et al.* 1980). Humans are exposed to arsenic (As) from many sources such as food, water, air, and soil; food is the major exposure source for As. USFDA (1993) in examining the food category indicated that fish and other seafood account for 90% of the total food As exposure with all other foods accounting for the remaining 10%. Donohue and Abernathy (1999) reported that the total As in marine fish, shellfish, and freshwater fish tissues ranged from 0.19–65, 0.2–125.9, and 0.007–1.46 μg/g dry wt, respectively.

Chen *et al.* (2001) indicated that long-term exposure to ingested inorganic As in groundwater has been found to induce blackfoot disease (BFD), a unique peripheral vascular disease that ends with dry gangrene and spontaneous amputation of affected extremities in southwestern coastal area of Taiwan, consisting mainly of four towns, Putai, Yichu, Hsuehchia, and Peikangtzu located at Chiayi and Tainan counties. There exists a dose-response relationship between As concentration in drinking water and risk of BFD. Recently, a number of studies on acquired and genetic susceptibility to As have been carried out in the BFD-endemic areas of southwestern Taiwan to find out the cause of BFD (Chen *et al.* 2001). Nowadays, most of the people living in these areas do not drink water from groundwater because tap water has been made available in this area. However, groundwater is still used for aquaculture.

Lin *et al.* (2001), Singh (2001), and Liao *et al.* (2002) conducted a long-term investigation during 1998–2001 in BFD area and indicated that As has been detected in many aquacultural ponds and that As concentrations in aquacultural waters are reported to range from 26.3 ± 16 to 251.7 ± 12.2 μg/L, whereas As concentrations in cultured fish ranged from 0.94 ± 0.3 to 15.1 ± 8.2 μg/g dry wt. The results are much greater than the maximum contaminant level (MCL) for As in drinking water of 50 μg/L. Han *et al.* (1994, 1996, 1998) reported that the consumption of contaminated seafood has been as an important route of human exposure to heavy metals (As, Cu, Zn, Pb, Cd, Hg) in Taiwan in that oyster (*Crassostrea gigas*) and other seafood (e.g., tilapia, tuna, and shrimp) are the most popular seafood. Farming of tilapia (*Orechromis mossambicus*) and large-scale mullet (*Liza macrolepis*) is a promising aquaculture in the BFD area because of high market

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value. The fish are fed with artificial bait, which does not contain As. These fish are maintained in the ponds for at least eight months (from March to October) before they go to the marketplace. If waterborne As levels are elevated, toxicity can occur and have severe effects on the health of cultured fish, which will reduce market prices and cause closure of fish farms.

Han *et al.* (1998) used a deterministic risk analysis method to estimate target hazard quotients and potential health risks for metals by consumption of seafood in Taiwan. Deterministic results, however, may hide significantly different levels of conservatism in relation to the uncertainty and variability present in each exposure parameter. Vermeire *et al.* (2001) pointed out that probabilistic modeling has received increasing support as a promising technique for characterizing uncertainty and variation in exposure estimates to environmental contaminants. To date, however, only a limited number of risk assessments regarding aquacultural management have incorporated probabilistic analyses. A predictive assessment is needed to evaluate the potential for As bioaccumulation, toxic effects to fish, and risks to human health (Reinert *et al.* 1991).

The objective of this paper is twofold: (1) to conduct an environmental risk assessment for As-contaminated aquacultural fish farms to develop As exposure estimates for tilapia and large-scale mullet in BFD area, and (2) to address the uncertainties by using a probabilistic approach to risk characterization that yields quantitative estimates of the risks themselves. The implications for human health risk estimates for people including city residents and subsistence fishers who eat tilapia and large-scale mullet harvested from BFD area are also described.

Materials and Methods

Bioaccumulation Model

We used a first-order one-compartment model to describe uptake and elimination processes of fish exposed to As in an aquacultural pond and to calculate As concentration in fish over time. The first-order one-compartment model for the gain and loss of As accumulation in fish features constant biokinetic rates and constant water concentration. Accordingly, the dynamic behavior would be represented as shown in Equation 1:

$$\frac{dC_f(t)}{dt} = k_1 C_w - k_2 C_f(t), \tag{1}$$

where $C_f(t)$ is the time-dependent As concentration in fish (μg/g dry wt), t is the time of exposure (d), C_w is the dissolved As concentration in water (μg/mL), k_1 is the uptake rate constant from dissolved phase by fish (mL/g/d), and k_2 is the depuration rate constant for As in fish (d^{-1}).

We consider the steady-state condition in Equation 1 and solve for C_f:

$$C_f = \frac{k_1}{k_2} C_w = \mathrm{BCF} C_w, \tag{2}$$

where BCF $= k_1/k_2 = C_f/C_w$ is the equilibrium bioconcentration factor (BCF) for fish (mL/g). By incorporating distributions for input parameters, Equation 2 can be run probabilistically.

BCFs and Water Concentrations. Of the variables used to estimate the distributions of As concentration in fish, BCF and C_w in Equation 2 are considered random. Current literature was reviewed to develop probability distributions for BCFs and As concentrations in water. Data on As concentrations in pond water and fish tissue including gill, liver, muscle, intestine, and stomach were derived from the 1998–2001 field survey in BFD area by Singh (2001), Lin *et al.* (2001), and Liao *et al.* (2002). They chose three appropriate management practices fish farms for each sampling location. All cultured farms had similar feeding strategies. In this study, we chose Yichu, Hsuehchia, Peikangtzu, and Putai located at BFD area in southwestern coastal area of Taiwan as our study sites in that fish farms in Yichu, Hsuehchia, Peikangtzu were cultured tilapia (*O. mossambicus*), whereas Putai was cultured large-scale mullet (*L. macrolepis*). Minimum, mean, standard error, or maximum values of BCFs and water As concentrations were sorted to produce frequency distributions corresponding to each sampling site.

Statistical Analysis. The data were divided into a minimum of ten bins as equally as possible. Absolute and relative frequencies were calculated and distributions were plotted using bin midpoints. We used the chi-square (χ^2) and the Kolmogorov-Smirnov (K-S) statistics (Zar 1999) to optimize the goodness-of-fit of distributions. We employed @RISK (Version 4.5, Professional Edition, Palisade Corp., USA) to analyze data and to estimate distribution parameters. The @RISK generated p values for the χ^2 statistics and provided critical values of D_{max} for the K-S statistics to estimate α levels from 0.01 to 0.50. For optimization, $p \geq 0.05$ was considered good, $p = 0.05$–0.10 was acceptable and $p < 0.10$ was poor. The selected distribution type and parameters were based on statistical criteria, comparisons of distribution parameters, and visual interpretation of histograms. USEPA (1997) in guiding principles for Monte Carlo analysis indicated that fit in the vicinity of expected values and in the tails were important criteria.

Finely *et al.* (1994) and Thompson *et al.* (2000) indicated that the lognormal distribution is often considered the default in environmental analysis. Distributions were fit to polled BCF data and the selected lognormal distributions had the acceptable χ^2 fit and K-S fit in that optimizations using either statistics yielded geometric mean (gm) and geometric standard deviation (gsd) expressing as LN (gm, gsd) (Figure 1). Water concentrations were also characterized by lognormal distributions by appropriately transforming from normal distributions for the mean with uncertainties characterized by standard error of the mean expressing as N (mean, SE) (Figure 1).

Human Health Exposure and Risk Model

The methodology for estimation of target cancer risk (TR) and hazard quotient (HQ) used was provided in USEPA *Region III Risk-Based Concentration Table, January–June, 1996* (USEPA 1996).

The target cancer risk to adults is defined as shown in Equation 3:

$$\mathrm{TR} = \frac{C_f \times \left(\mathrm{CSF_{IRIS}}\left(\frac{\mathrm{BW}}{70\ \mathrm{kg}}\right)^{1/3}\right) \times \mathrm{IR}_f \times \mathrm{EF} \times \mathrm{ED}}{\mathrm{BW} \times \mathrm{AT}_c \times 10^3}, \tag{3}$$

where TR is the incremental individual lifetime cancer risk (dimensionless), $\mathrm{CSF_{IRIS}}$ is the oral carcinogenic slope factor from IRIS (Integrated Risk Information System, provided by US EPA) database $(\mathrm{mg/kg/d})^{-1}$, IR_f is the annualized fish ingestion rate (g/d), C_f is the As concentration in fish (μg/g), EF is the exposure frequency (d/yr), ED is the exposure duration (yr), AT_c is the averaging time for carcinogens (d), BW is the body weight (kg), and 10^3 is the unit conversion factor.

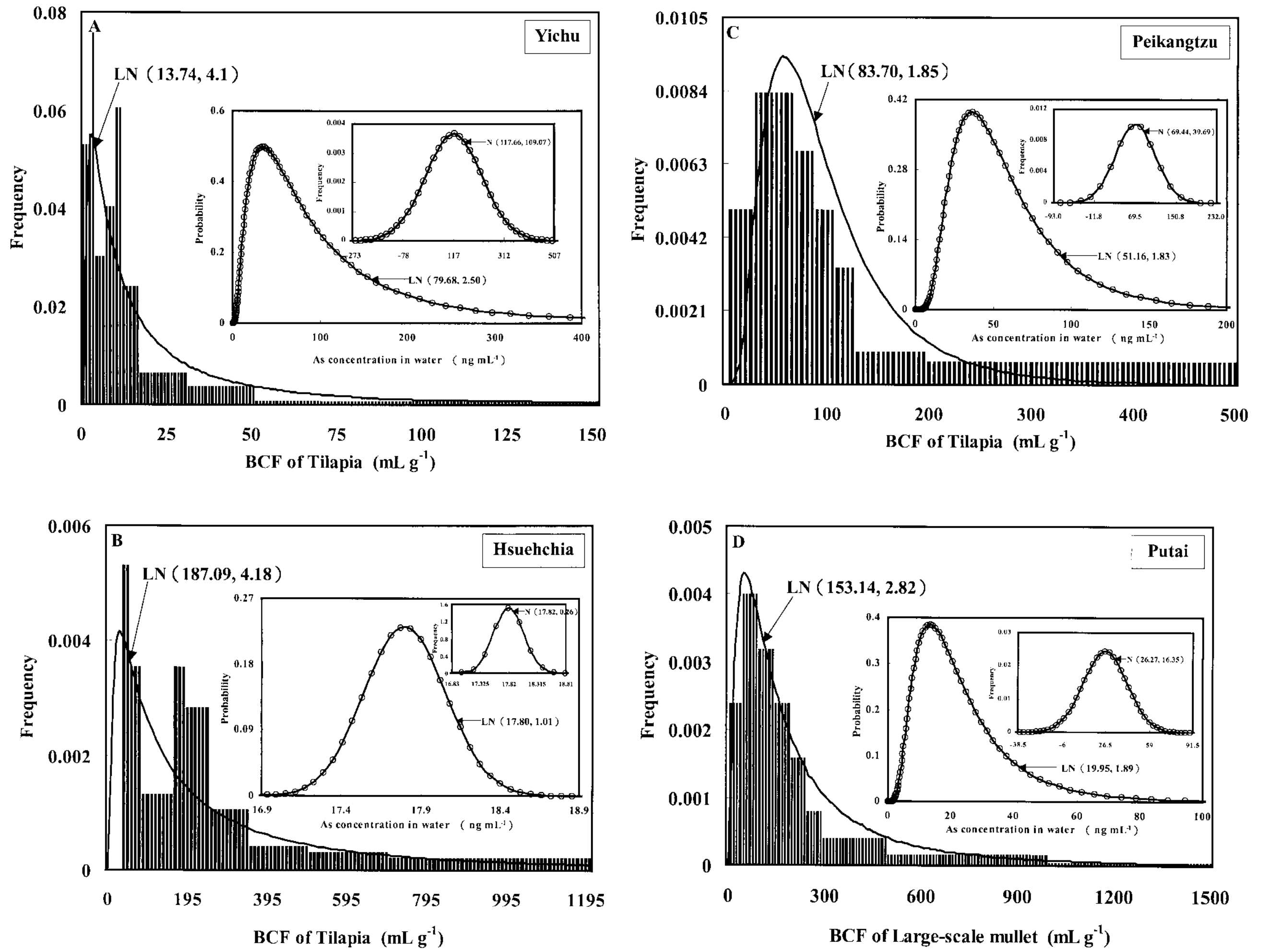

Fig. 1. Probability density functions of optimized lognormal distribution with geometric mean and geometric standard deviation as LN (gm, gsd) of BCFs and arsenic concentration in pond water for fish farms in (**A**) Yichu, (**B**) Hsuehchia, (**C**) Peikangtzu, and (**D**) Putai. The histograms of source data represented by frequency functions are also shown

The noncancer risk was estimated using the hazard quotient approach, defined as shown in Equation 4:

$$HQ = \frac{C_f \times IR_f \times EF \times ED}{\left(RfD_{IRIS} \left(\frac{BW}{70\ kg} \right)^{1/3} \right) \times BW \times AT_{nc} \times 10^3}, \qquad (4)$$

where HQ is the toxicity hazard quotient (dimensionless), RfD_{IRIS} is the oral reference dose from IRIS database (mg/kg/d), AT_{nc} is the averaging time for noncarcinogens (d), and 10^3 is the unit conversion factor. We treated C_f and IR_f in Equations 3 and 4 probabilistically.

Exposure Duration. The outputs of the bioaccumulation model are predictions of As concentrations in tissue of an individual fish over time. The exposure duration is defined as the exposure frequency of 365 d/yr for 30 yr (i.e., 10,950 d). The averaging time and number of fish consumed are required to provide input for an estimate of human health risk from exposure through fish ingestion. An averaging time of 365 d/yr for 70 yr (i.e., AT_c = 25,550 d) was used to characterize lifetime exposure for cancer risk calculation. An averaging time of 365 d/yr for 30 yr (i.e., AT_{nc} = 10,950 d) was used in characterizing noncancer risk.

Fish Ingestion. Data on fish consumption patterns were adapted from two sources: (a) Han *et al.* (1998), which was based on a brief questionnaire about seafood consumption frequency and weeks of consumption for 850 residents in Taipei city and (b) Lin (unpublished work), which was based on a questionnaire on tilapia and large-scale mullet daily consumption rate for 57 subsistence fishers in BFD area. Han *et al.* (1998) provided data for fish ingestion rates for adult consumption of cultured fish in Taipei city of Taiwan. The fish ingestion rates ranged from 10–30 and 35–70 g/d for 2–6 and 7–14 meals per week, respectively (Han *et al.* 1998). Lin (unpublished work) provided data on tilapia daily consumption rates for subsistence fishers in BFD area: 48–143 and 84–169 g/d for 2–6 and 7–14 meals per week, respectively. We approximated these data using a lognormal distribution and were transformed appropriately to ensure the data did not differ from a normal distribution before parametric analysis. Results give fish ingestion rate distributions of LN (14.56, 2.05) and LN (43.52, 1.87) for 2–6 and 7–14 meals per week, respectively, for Taipei city residents, whereas LN (104.79, 1.75), and LN (163.07, 2.61) for 2–6 and 7–14 meals per week, respectively, for subsistence fishers in BFD area. It was assumed in accordance with the USEPA (1989a) guideline that the ingested dose is equal to the absorbed contaminated dose and that

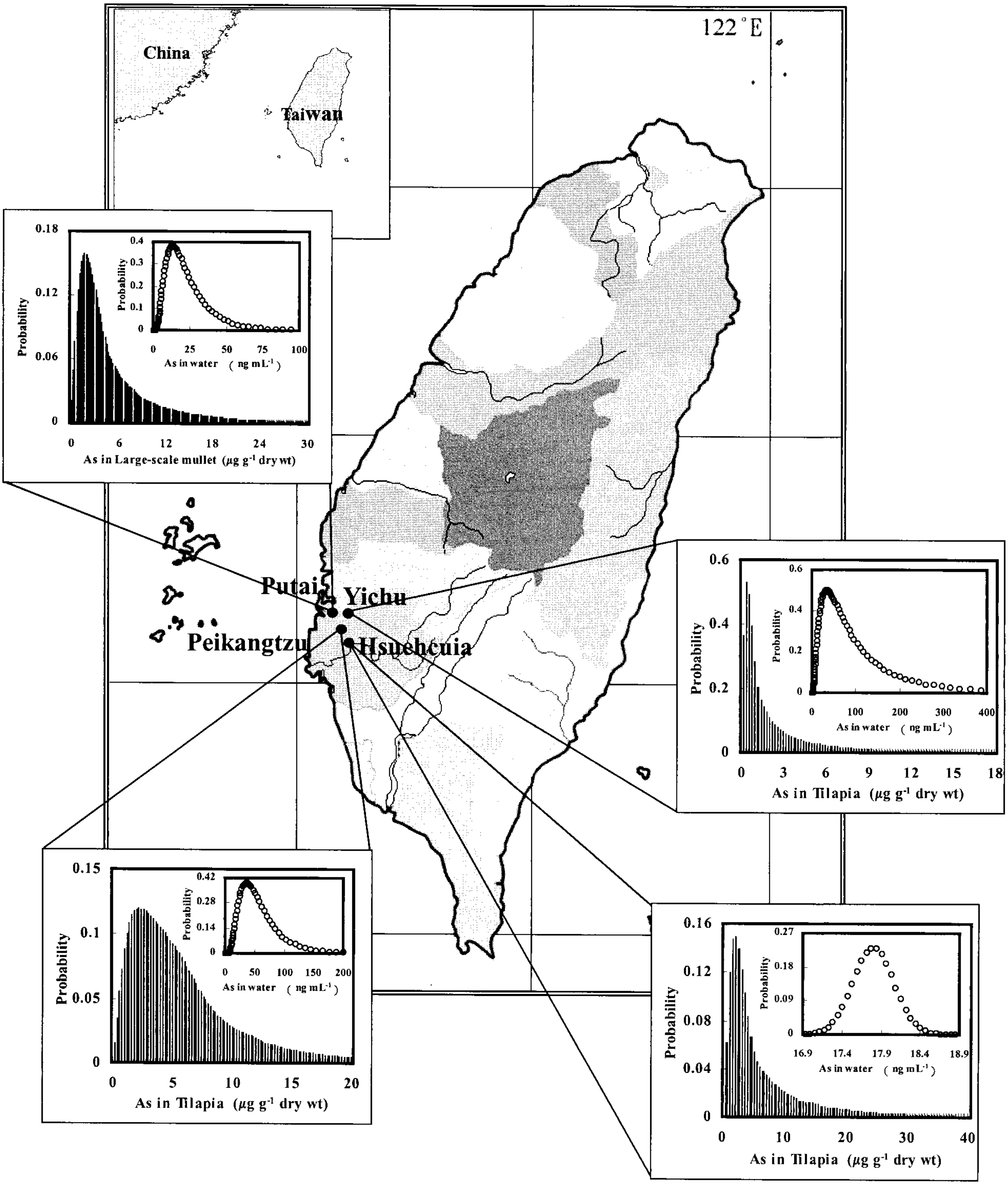

Fig. 2. Overall display of probabilistic distributions of predicted As concentrations in tilapia and large-scale mullet subject to measured water As concentration at four selected fish farms located at BFD area

cooking has no effect on the contaminants. Schoof *et al.* (1999) and Donohue and Abernathy (1999) reported that the amount of inorganic As in seafood ranged from <3–7% of the total As. In this work, we assume inorganic As accounts for 5% of the total As in seafood.

Body Weight. We used a 65 kg body weight for an average Taiwanese adult, as suggested by Han *et al.* (1998).

Toxicity Factors. The cancer slope factor and reference dose for ingested inorganic arsenic are 1.50 $(mg/kg/d)^{-1}$ and 3×10^{-4}

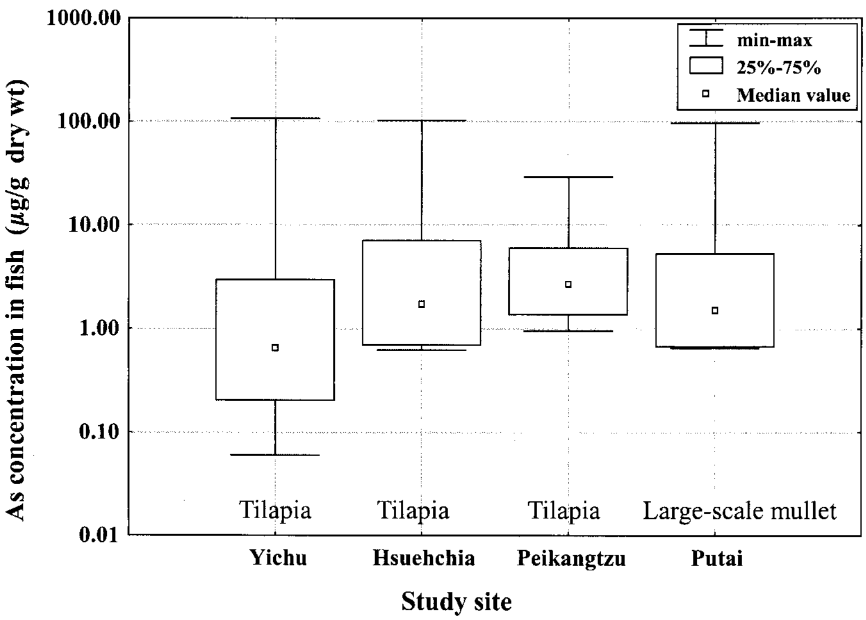

Fig. 3. Box and whisker plot representations of arsenic concentration in tilapia collected from fish farms in Yichu, Hsuehchia, and Peikangtzu, and in large-scale mullet collected from fish farms in Putai

mg/kg/d, respectively, provided by USEPA IRIS database (http://www.epa.gov/iris 2001) and normalized to account for extrapolation to a different body weight from the standard of 70 kg (Equations 3 and 4), as suggested in the *Exposure Factors Handbook* (USEPA 1997). These values are specified as point estimates following USEPA guidance (1989b).

Acceptable Risk Distribution. The acceptable risk distribution was assigned by constraints on percentiles. The lower end of the range of acceptable risk distribution is defined by a single constraint on the ninety-fifth percentile of risk distribution that must be equal or lower than 10^{-6} for carcinogens and equal or lower than 1 for noncarcinogens (Burmaster and Hull 1997).

Simulation Scheme

We used Equation 2 to predict As concentrations in cultured fish. Because the idea of the present model was to incorporate uncertainty into the model by selecting model parameters from lognormal probability distributions rather than experimentally derived values or field observations, we used a Monte Carlo technique to deal with the uncertainty (Vose 2000). To test the convergence and the stability of the numerical output, we performed independent runs at 1, 4, 5, and 10 thousand iterations with each parameter sampled independently from the appropriate distribution at the start of each replicate. Largely because of limitations in the data used to derive model parameters, inputs were assumed to be independent. The coefficient of variation (the ratio of standard deviation to mean for each number of iterations) was computed, with the conclusion that 5,000 iterations are sufficient to ensure the stability of results. In this case, the numerical error on the ninety-fifth percentile is equal to 2%. Sokal and Rohlf (1995) also indicated that more than 1000 replicate simulations gives K-S 95% confidence limits of approximately $\pm$4% on output distributions and should be sufficient to ensure reliable results.

Results and Discussion

Figure 2 illustrates the predicted probability density functions (pdfs) of As contents in tilapia and large-scale mullet subject to measured pdfs of pond water As concentrations from the four selected fish farms in the BFD area. Probabilistic simulations of the bioaccumulation models produced skewed distributions of predicted As concentrations in fish. Percentile predictions of As contents in fish could be determined from cumulative density functions (cdfs) corresponding to pdfs shown in Figure 2. Figure 3 shows box plots of interquartile and fiftieth-percentile predictions associated with whisker plots indicating measured minimum and maximum values of As concentrations in tilapia and large-scale mullet in the BFD area.

Figures 4 and 5 compare hazard quotient (HQ) and target cancer risk (TR), respectively, for human consumption of tilapia and large-scale mullet by Taipei city residents and subsistence fishers in the BFD area, respectively. The x-axis represents fish consumption rates along with fish farms in the BFD area in which the cultured fish goes to marketplace, whereas y-axis shows HQ and TR resulting from fish consumption by human under various meals per week. Under most regulatory programs, a HQ exceeding 1 and a TR between 10^{-4} and 10^{-6} indicate potential risk (Yost and Schoof 1995). Box and whisker plots represent the distribution of risks corresponding to the people who live in Taipei city and subsistence fishers who eat the cultured fish harvested from fish farms in BFD area.

Figure 4 shows that for Taipei city residents, a 95% probability or less experiencing a HQ less than 1 for daily consumption rate of 10–30 g/d, indicating that these probability distributions are acceptable; whereas most of the HQs are larger than 1 for 35–70 g/d fish consumption rate. All 95% probabilities of TR are larger than 10^{-6}, indicating unacceptable probability distributions for Taipei city residents (Figure 4). For subsistence fishers in the BFD area, 95% probability HQs or TRs are larger than 1 or much fall outside the range of 10^{-6}–10^{-4}, indicating high potential health risks (Figure 5). Han *et al.* (1998) reported that HQs caused by consuming fish containing As ranged from HQ = 0.136–0.340 for fish consumption rates of 10–70 g/d in that they assumed inorganic As constitutes 10% of total arsenic in seafood. Han *et al.* (1998) also indicated

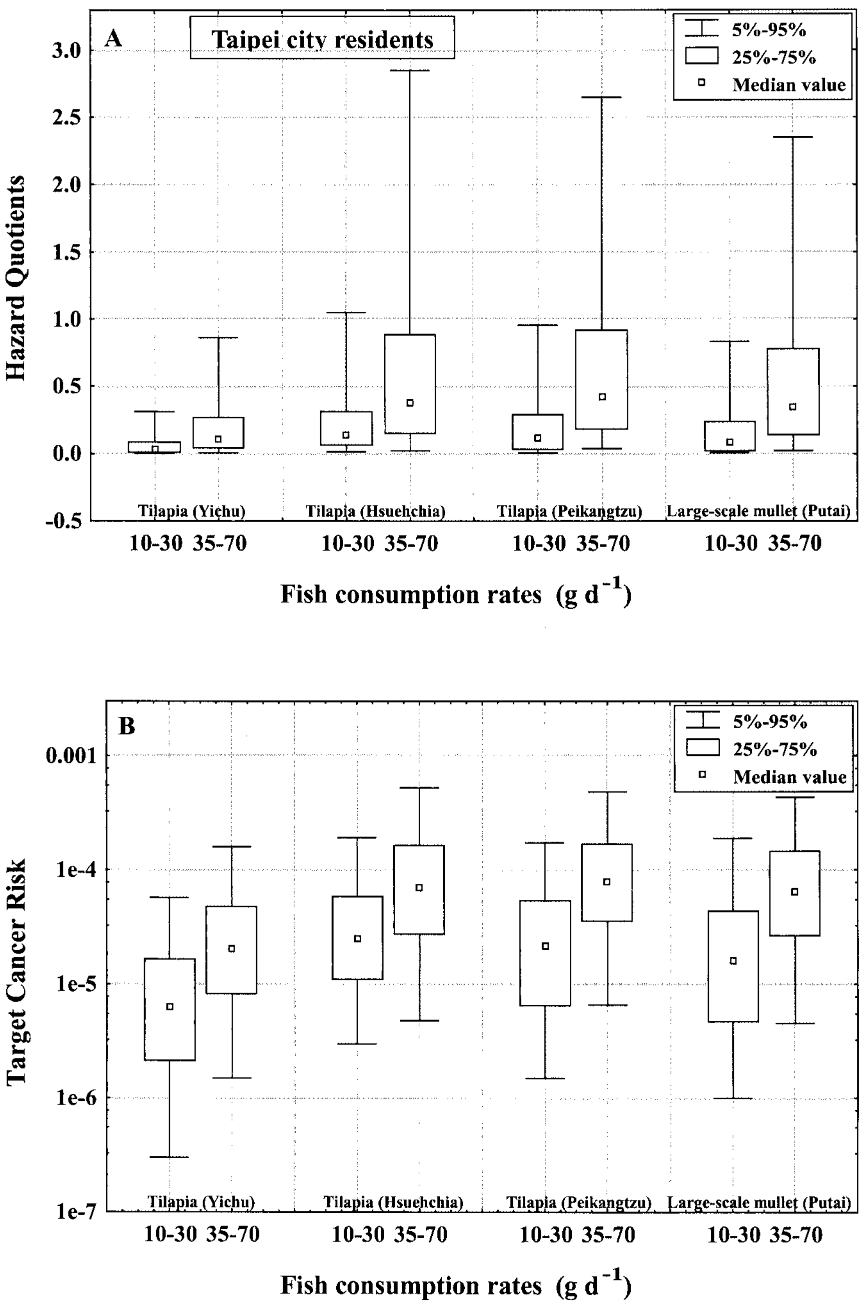

Fig. 4. Hazard quotients and target cancer risks for human consumption of tilapia and large-scale mullet harvested from fish farms in the BFD area under different fish consumption rates for Taipei city residents. Box and whisker plots are used to represent the uncertainty in risk estimates for each ranged fish consumption rate

that HQ does not define a dose-response relationship, and hence its numerical value should not be regarded as a direct estimate of risk. Han *et al.* (1998) further indicated that cancer risk estimates for consumption of inorganic As in fish from the BFD area ranged between TR $= 10^{-5}$ and 10^{-4} for fish consumption rates of 10–70 g/d, indicating high potential human health risks.

If compared with the acceptable ninety-fifth percentile probability of exceeding a 10^{-6} TR and 1 HQ, we can calculate the maximum allowable fish residual level associated to a standard unit fish concentration. The allowable residual concentration for chemical was calculated according to one of the methods suggested by Edelmann and Burmaster (1997) here briefly explained: the acceptable risk distribution is defined by a single constraint on the ninety-fifth percentile of the risk distribution that must be equal or lower than 10^{-6} for carcinogens and 1 for noncarcinogens. The TR and HQ distributions associated to a unit fish concentration of inorganic As were rescaled so that the ninety-fifth percentile is 10^{-6} for carcinogens and 1 for noncarcinogens. The calculated allowable fish residue is equal to f times the unit fish concentration where $f_i = 10^{-6}/R_i^{95}$ for the ith carcinogen and $f_i = 1/\mathrm{HQ}_j^{95}$ for jth noncarcinogen; R^{95} is the ninety-fifth percentile of the TR distribution and HQ^{95} is the ninety-fifth percentile of the HQ distribution associated to a unit fish residue level.

The maximum allowable residual concentrations of inor-

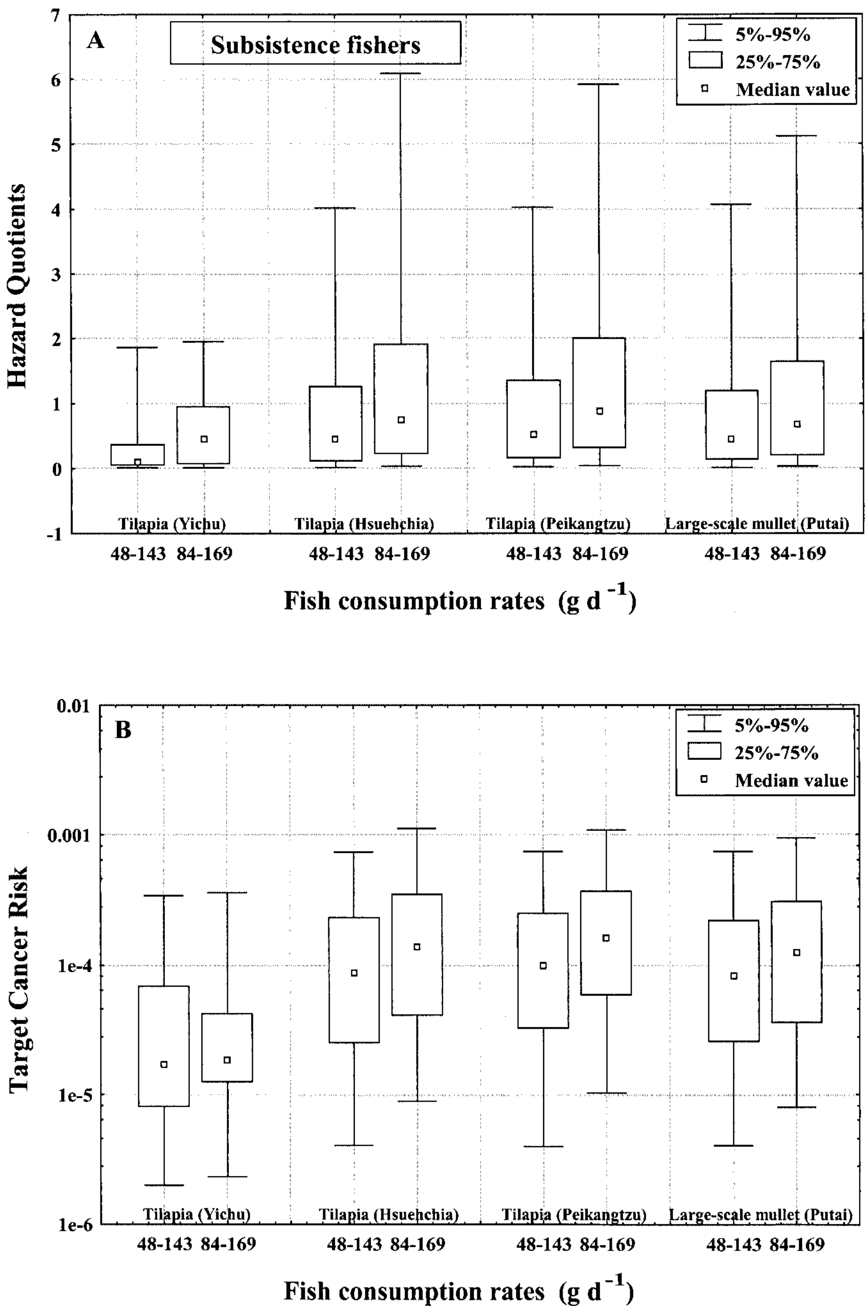

Fig. 5. Box and whisker plots representation of hazard quotients target cancer risks for human consumption of tilapia and large-scale mullet for subsistence fishers in the BFD area for each ranged fish consumption rate

ganic As in tilapia and large-scale mullet are 0.0019–0.0175 and 0.0023–0.0053 μg/g dry wt, respectively, for Taipei city residents under consumption rates of 10–70 g/d; whereas 0.0009–0.0029 μg/g dry wt, respectively, for subsistence fishers in the BFD area under consumption rates of 48–169 g/d; based on the ninety-fifth percentile probability exceeding a 10^{-6} TR or 1 HQ (Table 1). Table 1 also indicates that the risks associated with exposure by consuming tilapia harvested from Hsuehchia fish farms in allowable residual concentrations have a greater likelihood of occurrence than the same risks associated with exposure to the other study sites. This information implies that the mean value chosen in the deterministic bioaccumulation model for BCFs contribution to As accumulation in fish may not be sufficiently conservative: they will lead to target residual levels (see Table 1) associated with a probability of exceeding a 10^{-6} TR or 1 HQ, higher than the threshold considered acceptable in the probabilistic context. For example, if the mean BCF value corresponds to the 75% percentile of this parameter distribution, the allowable concentrations for inorganic As in fish are strongly influenced by BCF, and the resulting 75% level of conservatism implied in the mean value is insufficient to ensure a 95% level of conservatism in the target risk value of 10^{-6} calculated in the deterministic context.

Risk assessments provide risk managers with estimates to evaluate potential human health risks associated with exposure to contaminations in cultured fish. Food chain models often use the average concentration in contaminated media without considering the uncertainty and variability behavior of the recep-

Table 1. Calculated probabilistic maximum allowable fish residual levels for inorganic arsenic in BFD area in Taiwan

Study site	Fish	Fish consumption rate (g/d)	Probabilistic allowable fish residue (μg/g dry wt)[a]	
			Carcinogenic	Noncarcinogenic
Yichu	Tilapia	10–30[b]	0.0175	3.23
		35–70[b]	0.0063	1.16
		48–143[c]	0.0029	0.54
		84–169[c]	0.0028	0.51
Hsuehchia	Tilapia	10–30	0.0052	0.95
		35–70	0.0019	0.35
		48–143	0.0014	0.25
		84–169	0.0009	0.16
Peikangtzu	Tilapia	10–30	0.0058	1.05
		35–70	0.0021	0.38
		48–143	0.0014	0.25
		84–169	0.0009	0.17
Putai	Large-scale mullet	10–30	0.0053	1.20
		35–70	0.0023	0.43
		48–143	0.0013	0.25
		84–169	0.0011	0.19

[a] A standard unit fish concentration of inorganic As (1 μg/g dry wt) is considered.
[b] Ranged fish consumption rates for Taipei city residents (Han *et al.* 1998).
[c] Ranged fish consumption rates for subsistence fishers in BFD area (Lin, unpublished work).

tors. USEPA guidance explicitly requires that risk assessments address uncertainty in the underlying assumptions (USEPA 1989). The present analysis shows that BCFs of fish and concentrations of As in pond water are important components in evaluating realistic exposure and risk to human. We have represented a model that is useful in examining these factors and provides a simple model framework for incorporating realistic assumptions into risk estimates. Our approach does not ignore the possibility that some individuals may ingest fish that has been cultured mostly in the contaminated area. The advantage of the approach is that it assigns a probability to the occurrence of this scenario.

In conclusion, this paper illustrates the use of a simple bioaccumulation model in risk analysis. If used in a realistic fashion, it can more fully inform the decision-making process for the management of contaminated fish and can help support aquacultural water management decision making by providing a quantitative expression of the confidence in risk estimates. The model could be also modified to incorporate additional complexities and numbers of sites and contamination profiles. The ability to use and interpret such models, however, is often limited by the state of knowledge concerning the spatial/temporal behavior of aquacultural ecosystems. Nevertheless, probabilistic treatment of the model parameters, coupled with sensitivity analyses, should provide a rigorous basis for making sound environmental decisions. With proper application of risk communication, we can increase human understanding of fish consumption strategies, and we can channel this legitimate concern into actions that will result in stricter water quality regulations. The end result of such action will improve the water quality, which will benefit the health of the fish and the health of the people who eat them.

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