Risk characterization and exposure assessment in arseniasis-endemic areas of Taiwan

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Abstract

This paper examines the age-specific human health risks exposed to inorganic arsenic through arsenic-contaminated farmed fish/shrimp and groundwater consumptions in arseniasis-endemic areas of blackfoot disease (BFD)-endemic area and Lanyang Plain in Taiwan, based on a probabilistic integrated risk assessment framework. We employ an age-dependent predictive physiologically-based pharmacokinetic model to account for arsenic concentrations in target organs. We reconstruct age-specific dose-response profiles for arsenicosis and arsenic-induced cancers by best fitting a pharmacodynamics-based three-parameter Hill equation model to published epidemiological data from West Bengal and Taiwan. The predicted median arsenic concentrations in age group-specific skin, lung, and bladder ranged from $2.24 \text{–} 5.70 \mu g \text{g}^{-1}$ in BFD-endemic area, whereas $4.98 \text{–} 12.04 \mu g \text{g}^{-1}$ in Lanyang Plain, respectively. Risk analysis indicates that consumption of arsenic-contaminated farmed fish/shrimp and groundwater in arseniasis-endemic areas may increase threat to prevalence of arsenicosis for all age groups, whereas adults may undergo potential risks of arsenic-induced skin, lung and bladder cancers. We show that peoples in Lanyang Plain are more readily associated with higher morbidities for arsenicosis and skin cancer as well as fatalities for lung and bladder cancers than that of peoples in BFD-endemic area. Here we report the first case in which theoretical human health risks for consuming As-contaminated farmed fish/shrimp and groundwater in the arseniasis-endemic areas are alarming under a conservative condition based on a probabilistic risk assessment framework.

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Keywords: Arsenic; Probabilistic risk assessment; Physiologically-based pharmacokinetic; Pharmacodynamic; Arseniasis-endemic; Farmed fish/shrimp

1. Introduction

Systemic and chronic 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 (ATSDR, 2000; USEPA, 2002a,b). Inorganic arsenic is a human carcinogen, and ingestion of inorganic arsenic increases the risk of developing cancer of the bladder, liver, kidney, and skin (Abernathy et al., 2003; Yu et al., 2003). The clinical manifestations of chronic arsenic intoxication are referred to as arsenicosis (hyperpigmentation and keratosis). Arseniasis-endemic areas are referred to the areas situated at southwestern of BFD-endemic area and northeastern of Lanyang Plain of Taiwan region (Hsueh et al., 2003; Tsai et al., 2003; Yang et al., 2003; Chen et al., 2004). The pathway of arsenic exposure to residents at BFD-endemic area is through the consumption of farmed fish mainly including tilapia (Oreochromis mossambicus), milkfish (Chanos chanos), and large-scale mullet (Liza macrolepis), whereas at Lanyang Plain, the routines of arsenic exposure include farmed smelt (Plecoglossus altivelis) and grasp shrimp (Penaeus monodon) consumption and groundwater ingestion. Farmed fish/shrimp were bioaccumulated certain amounts of arsenic from aquaculture-used As-contaminated groundwater (Lin et al., 2001; Liao et al., 2003; Lin and Chiang, 2002).

USEPA (2002a,b) addressed children’s responses to environmental toxicants will be affected in which their systems absorb, distribute, metabolize and excrete chemicals. Because
of variability in physiology and behaviors, exposures are different among population of different age groups (Ginsberg et al., 2004). In this work, we examined the variability of the exposure risk across the population to improve accuracy of assessment pertaining to the age group-specific health.

We coupled an age-dependent predictive physiologically-based pharmacokinetic (PBPK) model to estimate arsenic concentration distributions in human blood, lung, bladder, skin, GI tract. A pharmacodynamic (PD)-based Hill equation model was employed to reconstruct age-specific dose-response functions for arsenicosis (hyperpigmentation and keratosis) and arsenic-induced cancers (skin, lung, and bladder cancers) based on published epidemiological data from West Bengal and Taiwan.

We combined the age-specific arsenic distributions in target organs and the reconstructed dose-response profiles to predict and to compare the arsenic exposure risks for children, adolescents, and adults through farmed fish/shrimp and groundwater consumption in arseniasis-endemic areas. We characterized the risk quantitatively by development of a probabilistic integrated assessment (PIA) framework that is most needed to interpret the prevalence of hyperpigmentation, keratoses, and skin cancer in which the health effect is morbidity, whereas fatality endpoint is for the incidence of lung and bladder cancers (NRC, 2001; Yu et al., 2003). The PIA framework are more valuable for communicating an accurate view of current scientific knowledge to those seeking information for decision-making than assessments that do not attempt to present results in a probabilistic framework.

The specific objective of this study is twofold: (1) to quantitatively estimate the inorganic arsenic distributions in human specific target organs by linking an age-dependent PBPK model and a PD-based age-specific dose-response model of noncancer/cancer effects and (2) to conduct a PIA-schemed approach based on the U.S. EPA paradigm (USEPA, 1998) to assess inorganic arsenic exposure risks to children, adolescents, and adults through consumption of popular farmed fish/shrimp and ingestion of groundwater in BFD-endemic area and Lanyang Plain.

2. Materials and methods

2.1. Arsenic levels in farmed fish from BFD-endemic area

Liao et al. (2003) and Lin et al. (2001) have conducted a field bioaccumulation investigation in tilapia farms in BFD-endemic area and reported that the mean arsenic pond water concentrations ranged from 26.3 ± 16 (mean ± sd) to 251.7 ± 12.2 μg L⁻¹, whereas the mean arsenic concentration in tilapia tissues were 29.3, 10.9, 53.7, 50.4, and 3.55 μg g⁻¹ dry wt in intestine, stomach, liver, gill, and muscle, respectively. Huang et al. (2003) have also collected samples of smelt and grass shrimp from seven culture ponds in Lanyang Plain and reported that the levels of arsenic in smelt and grass shrimp were 25.6 and 16.65 μg g⁻¹ dry wt, respectively. Due to the available information is scarce, we assumed that inorganic arsenic is also 5% of the total arsenic in smelt. For shrimp, on the other hand, Larsen et al. (1997) reported that inorganic arsenic was estimated to be 1.6% of the total arsenic in shrimp.

Chiou et al. (2001) noted that the variation in arsenic level in groundwater at Lanyang Plain was much more striking than the arsenic level in groundwater at BFD-endemic area. They further pointed out that the main exposure to inorganic arsenic in BFD-endemic areas is not only from consumption of fish but also from ingestion of groundwater in areas with arseiasis-endemic areas. We coupled an age-dependent predictive physiologically based pharmacokinetic (PBPK) model to estimate arsenic concentration distributions in human blood, lung, bladder, skin, GI tract. A pharmacodynamic (PD)-based Hill equation model was employed to reconstruct age-specific dose-response functions for arsenicosis (hyperpigmentation and keratosis) and arsenic-induced cancers (skin, lung, and bladder cancers) based on published epidemiological data from West Bengal and Taiwan.

2.2. Arsenic levels in farmed fish/shrimp and groundwater at Lanyang Plain

Recently, several articles have been devoted to the study of human health effects from arsenic exposure in Lanyang Plain (Hsueh et al., 2003; Tsai et al., 2003; Yang et al., 2003; Chen et al., 2004). Because of the abundance of underground water in the area, residents in Lanyang Plain have been using groundwater from shallow wells (<40 m in depth) since the late 1940 in that arsenic levels in groundwater ranged from undetectable (<0.15 μg L⁻¹) to 3590 μg L⁻¹ (Chiou et al., 2001). Although the implementation of a tap-water system was begun in Lanyang Plain in the 1990s, some residents around 50% still drank the arsenic-contaminated groundwater or used for aquaculture (Lin and Chiang, 2002).

Lin and Chiang (2002) have conducted a field investigation to analyze the arsenic levels in groundwater located at Tungsha and Wuchieh in Lanyang Plain, indicating that there were 64.4% of 180 groundwater samples were higher than the Taiwan drinking water standard (10 μg L⁻¹), whereas the maximum concentration of arsenic was 1145 μg L⁻¹. Lin and Chiang (2002) also have collected samples of smelt and grass shrimp from seven culture ponds in Lanyang Plain and reported that the levels of arsenic in smelt and grass shrimp were 25.6 and 16.65 μg g⁻¹ dry wt, respectively. Due to the available information is scarce, we assumed that inorganic arsenic is also 5% of the total arsenic in shrimp. For shrimp, on the other hand, Larsen et al. (1997) reported that inorganic arsenic was estimated to be 1.6% of the total arsenic in shrimp.

Chiou et al. (2001) noted that the variation in arsenic level in groundwater at Lanyang Plain was much more striking than the arsenic level in groundwater at BFD-endemic area. They further pointed out that the main exposure to inorganic arsenic in BFD-endemic areas is not only from consumption of fish but also from ingestion of groundwater in areas with arseiasis-endemic areas. We coupled an age-dependent predictive physiologically based pharmacokinetic (PBPK) model to estimate arsenic concentration distributions in human blood, lung, bladder, skin, GI tract. A pharmacodynamic (PD)-based Hill equation model was employed to reconstruct age-specific dose-response functions for arsenicosis (hyperpigmentation and keratosis) and arsenic-induced cancers (skin, lung, and bladder cancers) based on published epidemiological data from West Bengal and Taiwan.

Fig. 1. Schematic diagram of physiologically based pharmacokinetic (PBPK) model for As in human organs in that a PBPK model structure consists of lung, bladder, skin, and GI tract that interconnected by blood circulation.
arsenic of local residents in Lanyang Plain was through groundwater ingestion. We used the reported data from ROCPEA (2004) to estimate the arsenic levels in groundwater from significant arsenic-contaminated areas of Tungsha, Wuchihe, and Chuangwei in Lanyang Plain. Our analysis shows that the mean arsenic level in groundwater ranged from undetectable (<0.5 µg L\(^{-1}\)) to 373 µg L\(^{-1}\). Huang et al. (2003) reported that the inorganic arsenic level was measured to be 87.34% of the total arsenic in groundwater.

2.3. Age-dependent PBPK model

An age-dependent PBPK model was used to estimate inorganic arsenic distributions in specific human target organs through arsenic-contaminated farmed fish/shrimp and groundwater consumptions for different age groups. The PBPK model structure features lung (compartment 2), bladder (compartment 3), skin (compartment 4), and GI tract (compartment 5), which are interconnected by blood (compartment 1) circulation (Fig. 1). The essence of almost all PBPK models can be described by a linear dynamic equation (Yu, 1999a,b; Lien et al., 2001; Leggett et al., 2003; Gentry et al., 2004),

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

where \([C_{H}(t)]\) is a state matrix which describes the chemical concentration in each assigned human target organ \(i\), \([u(t)]\) represents an input vector of chemical concentration in farmed fish/shrimp or groundwater, \([K]\) is a state matrix which describes the diffusion exchange rate between target organs based on Fig. 1, and \([X]\) is a constant input matrix describes the exchange rate into the target organ,

\[
[X] = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}
\]

A steady-state condition is assumed in Eq. (1). Solving for the equilibrium arsenic concentrations in human lung (\(C_2\)), bladder (\(C_3\)), and skin (\(C_4\)),

\[
C_2 = \frac{Q_2 F_{O2} \text{IgC}}{[\text{AFH]}\text{I}](\text{HIJQ}_2F_D + \text{FIJQ}_2F_D + \text{FHJDQ}_2F_D + \text{FHIEQ}_2F_D)}
\]

(2)

\[
C_3 = \frac{Q_3 F_{O3} \text{IgC}}{[\text{AFH]}\text{I}](\text{HIJQ}_3F_D + \text{FIJQ}_3F_D + \text{FHJDQ}_3F_D + \text{FHIEQ}_3F_D)}
\]

(3)

\[
C_4 = \frac{Q_4 F_{O4} \text{IgC}}{[\text{AFH]}\text{I}](\text{HIJQ}_4F_D + \text{FIJQ}_4F_D + \text{FHJDQ}_4F_D + \text{FHIEQ}_4F_D)}
\]

(4)

where

\[
A = F_{O1}(Q_2 + Q_3 + Q_4), \quad B = Q_2 R_2^{-1}, \quad C = Q_3 R_3^{-1},
\]

\[
D = Q_4 R_4^{-1}, \quad E = Q_3 R_3^{-1}, \quad F = \text{IRaC}_{K_6} G = Q_3 R_3^{-1} + \text{IRaK}_T T,
\]

\[
H = Q_4 R_4^{-1} + K_5 \text{BW}_{i}, \quad \text{and} \quad I = Q_3 R_3^{-1} + K_6 W_{i},
\]

in that \(C_{Ka}\) is the arsenic concentration in farmed fish/shrimp (µg g\(^{-1}\) wet wt) or groundwater (µg L\(^{-1}\)); \(Q\) is the diffusive exchange rate of organ \(i\) (L d\(^{-1}\)); \(F_{Oi}\) is the binding coefficient of arsenic concentration to plasma proteins (g L\(^{-1}\)); \(R_i\) defines as \(C_i/C_{ai}\), 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 arsenic concentration in human target organ \(i\) (µg g\(^{-1}\)) and \(C_{ai}\) is the dissolved arsenic concentration in the blood leaving target organ \(i\) (µg mL\(^{-1}\)); IR is the daily farmed fish/shrimp ingestion rate (g d\(^{-1}\)) or groundwater daily ingestion rate (L d\(^{-1}\); BW is the whole body weight for population of different age group (g); \(W_i\) is the weight of human target organ \(i\) (g); \(W_{bl}\) is the organ weight of bladder for age-specific population (g); \(\alpha\) is absorption efficiency of arsenic (%); \(T\) is time to 95% steady state in GI tract (d); \(K_u\) is the urine elimination rate (g g\(^{-1}\) d\(^{-1}\)); \(K_{ep}\) is the sweat elimination rate (g g\(^{-1}\) d\(^{-1}\)); \(K_{EF}\) is the fecal elimination rate (g g\(^{-1}\) d\(^{-1}\)). The input variables needed to simulate the arsenic level in major organs for human include human physiological parameters (\(Q_i, F_{Oi}, R_i, IR, BW_i, W_{ij}, \alpha, T\), bioinetic parameters (\(K_{Li}, K_{Si}, K_{Ki}\)), and chemical parameter (\(C_{Ka}\)).

2.4. Age-specific dose-response profiles and risk models

We reconstructed age-specific dose-response models for morbidity and fatality effects versus arsenic level in human target organs by best fitting a PD-based three-parameter Hill equation model (Melnick et al., 1998) to the previously published dose-response functions expressed as the quadratic-exponential forms for arsenicosis and arsenic-induced cancers based on epidemiological data from West Bengal and Taiwan (Tables 1 and 2) (Yu et al., 2003). The Hill equation model was used because it allows comparison of cooperativity among different dose-response profiles that can validate the observations of published studies and can explicitly show the responses are dependent on the oncancer/cancer.
Incidence functions for a given organ-specific arsenic concentration in humans can be expressed as a joint probability function or exceedance profile, which describes the probability of exceeding the concentration associated with a particular degree of carcinogenic or noncarcinogenic effect,

\[ R(P_i) = F(C_{HI})F(P_i|C_{HI}), \]

(10)

\[ R(I_i) = F(C_{HI})F(I_i|C_{HI}), \]

(11)

where \( R(P_i) \) and \( R(I_i) \) are the prevalence and incidence risk for a specific organ \( i \) at concentration \( C_{HI} \), and \( F(C_{HI}) \) is the CDF of having organ concentration \( C_{HI} \).

### 2.5. Uncertainty and sensitivity analyses

In exposure and risk assessment, there are several sources of uncertainty. Due to inherent natural variability, model variables can be defined in terms of a probability density function that was derived from a limited set of observations. The data, however, may not be representative of the entire population, and sample statistics may not be accurate estimates of the true values of the population parameters. This leads to uncertainty in the parameter estimation procedures. To explicitly account for this uncertainty/variability and its impact on the estimation of expected risk, a Monte Carlo (MC) simulation was adopted. 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 result showed that 10,000 iterations were sufficient to ensure the stability of results.

A sensitivity analysis was conducted to identify the critical input variables that presented in the uncertainty and variability analysis of the PIA framework for human health assessment. The sensitivity of each variable relative to one another was assessed by calculating rank correlation coefficients between each input and output during simulations and then estimated each input contribution to the output variance by squaring the output variance and normalizing to 100%.

The MC simulation and sensitivity analysis were implemented using Crystal Ball® (Version 2000.2, Decisioneering, Inc., Denver, CO, USA). We used the Crystal Ball® tool in Crystal Ball® Professional Edition. The sensitivity of impact factors was estimated by the rank correlation method. The MC simulation was used for both the PIA framework and the sensitivity analysis. The number of iterations for each run was set to 10,000 iterations. 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 result showed that 10,000 iterations were sufficient to ensure the stability of results.

### Table 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Children (4–12 yrs)</th>
<th>Adolescents (13–18 yrs)</th>
<th>Adults (19–65 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, BW (kg)</td>
<td>TN(29.12, 7.39)</td>
<td>TN(54.21, 5.37)</td>
<td>TN(60.05, 4.26)</td>
</tr>
<tr>
<td>Bladder weight, ( W_{Bl} ) (g)</td>
<td>TN(177.70, 45.74)</td>
<td>TN(270.64, 53.93)</td>
<td>TN(289.93, 55.63)</td>
</tr>
<tr>
<td>Ingestion rate, IR ( \text{Farmed seafood (g d}^{-1}) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ilipa</td>
<td>LN(16.57, 1.36)</td>
<td>LN(25.96, 1.24)</td>
<td>LN(27.82, 1.25)</td>
</tr>
<tr>
<td>Milkfish</td>
<td>LN(18.07, 1.37)</td>
<td>LN(28.31, 1.25)</td>
<td>LN(30.34, 1.25)</td>
</tr>
<tr>
<td>Large-scale mullet</td>
<td>LN(0.92, 1.37)</td>
<td>LN(1.44, 1.24)</td>
<td>LN(1.54, 1.25)</td>
</tr>
<tr>
<td>Smelt</td>
<td>LN(1.50, 1.36)</td>
<td>LN(2.34, 1.25)</td>
<td>LN(2.51, 1.25)</td>
</tr>
<tr>
<td>Grass shrimp</td>
<td>LN(0.20, 1.36)</td>
<td>LN(0.32, 1.24)</td>
<td>LN(0.34, 1.25)</td>
</tr>
<tr>
<td>Groundwater (L d(^{-1})</td>
<td>LN(1.27, 1.37)</td>
<td>LN(2.00, 1.24)</td>
<td>LN(2.14, 1.25)</td>
</tr>
</tbody>
</table>

\( a \) Exposure duration (median) — children: 8 yrs, adolescents: 16 yrs, adults: 42 yrs.

\( b \) Information adopted from DOH (2002) in that TN(m, sd) is a truncated normal distribution with mean (m) and standard deviation (sd).

\( c \) Adopted and estimated from Mann et al. (1996).

\( d \) Values were calculated from Fisheries Administration, Council of Agriculture (FACOA, 2004) and Department of Statistics (DOS, 2004). LN (gm, gsd) is a lognormal distribution with geometric mean (gm) and geometric standard deviation (gsd).
Table 4
Input chemical and biokinetic parameters to define distributions for Monte Carlo (MC) simulation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical parameter</td>
<td></td>
</tr>
<tr>
<td>Arsenic concentration in farmed seafood,</td>
<td></td>
</tr>
<tr>
<td>$C_{AS,w}$ (μg g$^{-1}$ wet wt)</td>
<td></td>
</tr>
<tr>
<td>Tilapia$^a$</td>
<td>LN(1.98, 1.56)</td>
</tr>
<tr>
<td>Milkfish$^b$</td>
<td>LN(3.60, 1.39)</td>
</tr>
<tr>
<td>Large-scale mullet$^c$</td>
<td>LN(0.57, 1.09)</td>
</tr>
<tr>
<td>Smelt$^d$</td>
<td>LN(6.37, 1.10)</td>
</tr>
<tr>
<td>Grass shrimp$^e$</td>
<td>LN(1.14, 1.10)</td>
</tr>
<tr>
<td>Arsenic concentration in groundwater,</td>
<td></td>
</tr>
<tr>
<td>$C_{AS,w}$ (μg L$^{-1}$)$^f$</td>
<td>LN(42, 1.99)</td>
</tr>
<tr>
<td>Biokinetic parameters</td>
<td></td>
</tr>
<tr>
<td>Urine elimination rate, $K_U$ (d$^{-1}$)</td>
<td>LN(1.79, 1.10)</td>
</tr>
<tr>
<td>Fecal elimination rate, $K_F$ (d$^{-1}$)</td>
<td>LN(0.029, 1.11)</td>
</tr>
</tbody>
</table>

a Value was taken from Liao et al. (2003).
b Value was taken from Lin et al. (2002).
c Value was taken from Lin and Chiang (2002).
d Value was taken from ROCPEA (2004).
e Value was taken from Yu (1999b).
f Values were taken from Yu (1999b).

incorporated probability distributions into MC simulation to obtained 2.5–97.5th percentiles as 95% CI for all uncertainty analyses.

2.6. Model parameterization

2.6.1. Physiological parameters: $BW$, $W_{1/3}$, $IR$

Distributions of the average body weight ($BW$) of Taiwanese children, adolescents, and adults were fitted to the data obtained from Department of Health (DOH), Taiwan (2002). Here, adults were defined as individuals from ages 19 to 65 yrs, adolescents were defined as individuals from ages 13 to 18 yrs, whereas children were defined as individuals from ages 4 to 12 yrs. To account for this uncertainty, we constructed truncated normal (TN) distributions based on ±10% for the input variables and had the optimal K$^2$ goodness-of-fit. We estimated average farmed fish/shrimp ingestion rate (IR) by dividing the annual consumption quantities and the trade of fishery import products of tilapia, milkfish, and large-scale mullet in BFD-endemic areas, and smelt and grass shrimp in Lanyang Plain by the number of local residents (age > 5 yrs) (FAOCA, 2004; DOS, 2004). The daily ingestion rate of groundwater (IR) was estimated 2 L d$^{-1}$ per person in Lanyang Plain. We approximated these data using a lognormal (LN) distribution. The $W_{1/3}$ and IR values were adjusted to the standard BW of TN(55.69 kg, 11.45) (ages range from 4–65 yrs) for children, adolescents, and adults (Meacher et al., 2002). For instance, $W_{1/3}$ can be calculated as $W_{1/3} = W_1 / (BW / TN(55.69, 11.45)^{0.33})$ (Table 3).

2.6.2. Chemical and biokinetic parameters: $C_{AS,S}$, $C_{AS,w}$, $K_U$, $K_F$ and $K_S$

Distributions of arsenic in tissues of tilapia, milkfish, and large-scale mullet, smelt, and grass shrimp were fitted to the polled field observations from arseniasis-endemic areas which measured by Liao et al. (2003), Lin et al. (2001, 2004), and Lin and Chiang (2002), and the selected LN distributions had the optimal K$^2$ and $\chi^2$ goodness-of-fit. Distribution of groundwater arsenic concentration in Lanyang Plain was best fitted to the published data obtained from ROCPEA (2004), and the selected LN distribution also had the optimal K$^2$ and $\chi^2$ goodness-of-fit. The estimated bladder and GI tract elimination rates were adopted from Yu (1999b). We assigned the parameters based on ±10% of base case values and the selected LN distributions had the acceptable $\chi^2$ and K$^2$ fits in that optimizations using either statistics yielded gm and gsd. Leggett et al. (2003) indicated that the elimination percentages for human in bladder, GI tract and skin were 0.85, 0.13, and 0.02, respectively, showing that the sweat elimination rate is much less than the elimination rates in bladder and GI tract. Hence, we ignored the sweat elimination rate (Table 4).

2.6.3. Dose-response parameters: $EC_{50}$ and $CSF_{corr}$

We estimated the probability distributions of age-specific $EC_{50}$ values for arsenocarcin and arsenic-induced cancers based on the published dose-response functions from Yu et al. (2003). The corrected cancer slope factors ($CSF_{corr}$) for dose-response functions of lung and bladder cancers were estimated based on the benchmark dose followed U.S. EPA approach (USEPA, 2000a,b) (Table 5).

3. Results and discussion

3.1. Multiple-pathway arsenic exposure assessment

Fig. 2 depicts the exposure profile of the box plots of interquartile and 50%-tile predictions associated with whisker plots indicating 10%- and 90%-tile predictions of arsenic contents in children, adolescents, and adults target organs from BFD-endemic area and Lanyang Plain. The estimated physiologically-based parameters of blood perfusion rate, partition coefficient, fraction arsenic dissolved in blood, time to 95% steady state in GI tract, and absorption efficiency among target organs in PBPK model were reported only as average values (Table 6). Results demonstrate that the distribution of arsenic concentration in human bladder is more highly skewed with a long tail at higher

Table 5
Input dose-response parameters for children, adolescents, and adults to define distributions for Monte Carlo (MC) simulation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Children (4–12 yrs)</th>
<th>Adolescents (13–18 yrs)</th>
<th>Adults (19–65 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Median$ effective concentration, $EC_{50}$ (μg g$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratosis$^a$</td>
<td>N(6.36, 0.883)</td>
<td>N(6.36, 0.883)</td>
<td>N(6.36, 0.883)</td>
</tr>
<tr>
<td>Hyperpigmentation$^b$</td>
<td>N(4.59, 1.197)$^b$</td>
<td>N(4.59, 1.197)</td>
<td>N(4.59, 1.197)</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>N(150.67, 69.77)</td>
<td>N(35.88, 3.60)</td>
<td>N(3.51, 0.17)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>–</td>
<td>N(2500, 489.99)</td>
<td>N(26.85, 5.51)</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>–</td>
<td>N(4260, 834.94)</td>
<td>N(34.47, 2.81)</td>
</tr>
</tbody>
</table>

$^a$ The $EC_{50}$ values for hyperpigmentation and keratosis are age-independent.

$^b$ N(m, sd) is a normal distribution with mean (m) and standard deviation (sd).
concentration, and estimated human bladder arsenic concentration has a higher uncertainty as quantified by the variance in BFD-endemic area and Lanyang Plain (Fig. 2). The arsenic levels in adult target organs are higher than those in children and adolescents. Fig. 2 also indicates that the arsenic contents of local residents living in Lanyang Plain are higher than those in BFD-endemic area. Since residence in Lanyang Plain drinks groundwater and residence from BFD-endemic area do not drink underground water. The inorganic arsenic level accounts for 87.34% of total arsenic in groundwater in Lanyang Plain, that are much higher than the seafood inorganic arsenic level (1.6–7%). This may explain in part why the As concentration in target organs at BFD-endemic area contaminated by As is lower than that of in Lanyang Plain.

The median arsenic concentrations among three age groups indicate that bladder has the highest range values of 5.11–20.71 and 11.07–43.45 μg g⁻¹ than those of in skin of 2.24–5.70 and 4.98–12.04 μg g⁻¹ and lung of 3.76–9.46 and 8.23–19.92 μg g⁻¹ in BFD-endemic area and Lanyang Plain, respectively. Lin et al. (2005) reported that tissue accumulations of inorganic arsenic in rabbit bladder after chronic dosing for 30 days had the highest value than that of in lung and skin. Hughes et al. (2003) also pointed out that the arsenic level in mice bladder had higher accumulation capacity after 9 and 17 repeated daily arsenate exposure.

### Table 6

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Symbol</th>
<th>Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood perfusion rate (L d⁻¹)ᵃ</td>
<td>Q₂</td>
<td>230.4</td>
</tr>
<tr>
<td>Lung</td>
<td>Q₃</td>
<td>1368</td>
</tr>
<tr>
<td>Bladder</td>
<td>Q₄</td>
<td>504.0</td>
</tr>
<tr>
<td>Skin</td>
<td>Q₅</td>
<td>1382.4</td>
</tr>
<tr>
<td>GI tract</td>
<td>Q₆</td>
<td>1382.4</td>
</tr>
<tr>
<td>Lung:blood Partition coefficient (L g⁻¹)ᵇ</td>
<td>R₂</td>
<td>4.15</td>
</tr>
<tr>
<td>Bladder:blood</td>
<td>R₃</td>
<td>4.15</td>
</tr>
<tr>
<td>Skin:blod</td>
<td>R₄</td>
<td>2.5</td>
</tr>
<tr>
<td>GI tract:blod</td>
<td>R₅</td>
<td>2.5</td>
</tr>
<tr>
<td>Fraction As dissolved in blood (g L⁻¹)ᶜ</td>
<td>F₀</td>
<td>0.2</td>
</tr>
<tr>
<td>Time to 95% steady state in GI tract (d)ᵈ</td>
<td>T</td>
<td>1</td>
</tr>
<tr>
<td>Absorption efficiency of As (%)ᵉ</td>
<td>α</td>
<td>85</td>
</tr>
</tbody>
</table>

ᵃ Values were taken from Mann et al. (1996) and Leggett et al. (2003).
ᵇ Values were taken from Yu (1999b).
ᶜ Adopted from Leggett et al. (2003).
ᵈ Estimated from Lawrence and Gobas (1997).
ᵉ Adopted from Caussy (2003).

3.2. Age-specific concentration-response relationships assessment

Here we combined the exposure distribution profiles and the reconstructed dose-response profiles to predict and to compare the human arsenic exposure risks for local residents in BFD-endemic area and Lanyang Plain, respectively. We fitted optimally the PD-based Hill equation model to published dose-response functions (Table 1, Fig. 3J–R) to obtain the reconstructed age-specific dose-response profiles (Fig. 4A–I) for arsenicosis and arsenic-induced cancers. The Hill equation model and a 10,000 MC simulation provided an adequate fit for the data ($\chi^2$ goodness-of-fit, $P > 0.5$).

The $n$ and EC₅₀ values clearly show that there were apparent differences in sensitivity to arsenic in children, adolescents, and adults health effects except arsenicosis. Yu et al. (2003) reported that the prevalence ratios of hyperpigmentation and keratosis do not change with age under constant concentrations, resulting in the $n$ and EC₅₀ values of hyperpigmentation and keratosis do not vary with age neither (Table 1 and Eq. (T-1)). Regression lines (Fig. 3A–I) from the nonlinear Hill three-parameter model transformations of published dose-response model (Table 1, Fig. 3J–R) had good fit as judged by $r^2$ values (0.857–0.998, $P < 0.05$). The Hill coefficients ($n$) for arsenicosis (1.344–1.402) from all...
Fig. 3. Reconstructed dose-response profiles with 95% confidence interval (CI) for relationships between human health effects and As concentration based on Hill equation model regarding arsenicosis of (A) hyperpigmentation, (B) keratosis, and As-induced cancers of (C)–(E) skin cancer for children, adolescents, and adults, (F), (G) lung and (H), (I) bladder cancers for adolescents and adults, as well as (J)–(R) the published dose-response models adopted from Yu et al. (2003) with 95% CI for arsenicosis and As-induced cancers.
population and for arsenic-induced cancers (1.29–4.11) from agespecific population are indicative of positive cooperatively ($n \geq 1$).

Fig. 3A and B show the calculated EC$_{50}$ values are 4.59 μg g$^{-1}$ (95% CI: 2.25–6.94) for hyperpigmentation and 6.36 μg g$^{-1}$ (95% CI: 4.63–8.09) for keratosis. For skin cancer, the median EC$_{50}$ values are 100, 36, and 3.2 μg g$^{-1}$ for children, adolescents, and adults, respectively. On the other
hand, the median EC₅₀ values for lung and bladder cancers are 2500 and 4300 μg g⁻¹ for adolescents, whereas 28 and 34 μg g⁻¹ for adults, respectively.

3.3. Morbidity and fatality risks

A probabilistic representation of risk curves shown in Fig. 4 were based on the exposure and effect profiles for people consumptions of farmed fish/shrimp and groundwater in BFD-endemic area and Lanyang Plain, respectively. Because of variability and uncertainty in model parameters from Eqs. (8) and (9) describing the exceedence CDFs associated with a particular degree of prevalence and incidence (Fig. 4), we applied the plotted probabilities calculated from the outcome of the MC simulation to estimate risks. In BFD-endemic area, the probabilities that 90% or more of local residents affected by keratosis (per 100,000 people) was approximately 9970 (95% CI: 7420–14,510), whereas 13,720 (95% CI: 8,180–30,230) by hyperpigmentation, i.e., the probability is 0.90 that at least 9970 (per 100,000) and 13,720 (per 100,000) of people will be affected by keratosis and hyperpigmentation, respectively (Table 7). Table 7 shows the exceedence risks (per 100,000) (risk = 0.90) of fatality effect for lung cancer in arseniasis-endemic area ranged from 1.76 × 10⁻⁴–2.68 × 10⁻⁴ for adolescents and 303–853 for adults, whereas for bladder cancer ranged from 1.94 × 10⁻⁵–4.50 × 10⁻⁵ for adolescents and 204–524 for adults.

The present risk analysis suggests that consumption of arsenic-contaminated farmed fish/shrimp and groundwater in arseniasis-endemic areas may increase threat to prevalence of arsenicosis for all age groups, whereas adults may undergo potential risks of arsenic-induced skin, lung and bladder cancers. (Fig. 4 and Table 7). Due to the difference in exposure duration of adults: 61 yrs (4–18 yrs) and adolescents: 12 yrs (4–65 yrs), the exceedence risk for adults is much higher than that of adolescents (Table 7). Most notably, we show that peoples in Lanyang Plain are more readily associated with higher morbidities for arsenicosis and skin cancer as well as fatalities for lung and bladder cancers than that of peoples in BFD-endemic area.

3.4. Sensitivity analysis

Sensitivity analysis indicates that the most important variables for human arsenic exposure are arsenic concentrations in farmed tilapia for

Table 7
Exceedence risk (per 100,000) (risk = 0.90) with 95% confidence interval (CI) in human health effects

<table>
<thead>
<tr>
<th></th>
<th>BFD-Endemic Area</th>
<th>Lanyang Plain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratosis</td>
<td>9970 (7420–14,510)</td>
<td>13,524 (10,201–19,231)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>13,720 (8180–30,230)</td>
<td>18,492 (11,374–37,628)</td>
</tr>
</tbody>
</table>

**Skin cancer**

<table>
<thead>
<tr>
<th></th>
<th>BFD-Endemic Area</th>
<th>Lanyang Plain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>37 (23–66)</td>
<td>37 (23–65)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>342 (272–374)</td>
<td>481 (382–526)</td>
</tr>
<tr>
<td>Adults</td>
<td>24,290 (19,860–29,870)</td>
<td>51,800 (45,370–58,810)</td>
</tr>
</tbody>
</table>

**Lung cancer**

<table>
<thead>
<tr>
<th></th>
<th>BFD-Endemic Area</th>
<th>Lanyang Plain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents</td>
<td>1.76 × 10⁻⁴ (1.04 × 10⁻⁷–3.33 × 10⁻⁴)</td>
<td>2.68 × 10⁻⁴ (1.58 × 10⁻⁴–5.08 × 10⁻⁴)</td>
</tr>
<tr>
<td>Adults</td>
<td>303 (179–577)</td>
<td>853 (504–1612)</td>
</tr>
</tbody>
</table>

**Bladder cancer**

<table>
<thead>
<tr>
<th></th>
<th>BFD-Endemic Area</th>
<th>Lanyang Plain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents</td>
<td>1.94 × 10⁻⁵ (1.12 × 10⁻⁵–3.84 × 10⁻⁵)</td>
<td>4.50 × 10⁻⁵ (2.59 × 10⁻⁵–8.85 × 10⁻⁵)</td>
</tr>
<tr>
<td>Adults</td>
<td>204 (110–418)</td>
<td>524 (286–1067)</td>
</tr>
</tbody>
</table>

If farmed fish is not contaminated by arsenic, it is the healthy food with valuable nutrients, such as omega-3 polyunsaturated fatty acid and muscle proteins, that are well known to have certain benefits to human health effects (Huang et al., 2004; Tokur et al., 2004). Our present study, however, indicates that consumption of arsenic-contaminated farmed fish/shrimp may pose potential arsenicosis and skin cancer risks. To precisely determine the risk/benefit ratios from consumption of farmed fish are complicated, cautious interpretation of present data may substantially reduce the likelihood in dealing with uncertainty and risk management.

Here we report the first case in which theoretical human health risks for consuming As-contaminated farmed fish/shrimp and groundwater in the arseniasis-endemic areas are alarming under a conservative condition based on a probabilistic risk assessment framework. We believe that the PIA framework – probabilistic PBPK/PD model together with risk diagrams – is an effective representation of state-of-the-art results of scientific assessments for human arsenic exposure through consumption of contaminated farmed fish/shrimp and groundwater. Despite the great uncertainty in many aspects of integrated assessment, the arsenic toxicity, arsenic concentration in farmed species or groundwater, and daily ingestion rates that may modify the outcomes of risk estimate, cautious interpretation of observations obtained from current epidemiological data can substantially reduce this likelihood.

Although the suitability and effectiveness of techniques for presenting uncertain results is context-dependent, we suggest that our probabilistic framework and methods can be taken seriously because...
they produce general conclusions that are more robust than estimates made with a limited set of scenarios or without probabilistic presentations of outcomes. Besides, our predictive risk modeling techniques also offers a risk-management framework for future discussion in deriving risk thresholds human arsenic exposure.

References

Abernathy CO, Thomas DJ, Calderon RL. Health effects and risk assessment of arsenic. J Nutr 2003;133:1536S–8S.


