Clarifications on the Draft 2010 Toxicological Review of Inorganic Arsenic (iAs; Cancer) for the Work Group of the Chartered SAB

A Work Group of the Chartered SAB (WG-SAB-iAs) met on April 6-7, 2010 to review the draft 2010 *Toxicological Review of Inorganic Arsenic (Cancer)*. During this public meeting, members of the Work Group requested additional clarification on several topics from U.S. EPA. The purpose of this note is to respond to this request.

U.S. EPA identified the following topics for which SAB requested clarification:

1) Taiwanese water consumption,
2) Non-water arsenic intake,
3) Southwest Taiwanese well arsenic concentrations,
4) Availability of the U.S. EPA (1989) memo (i.e., the Abernathy et al., 1989 memo),
5) Geographic locations of the reference populations, and
6) A rationale to explain greater increases in female bladder cancer compared to other cancers (i.e., female lung cancer and male lung and bladder cancers).

U.S. EPA has prepared clarifications on these topics which the SAB workgroup members may find useful in preparing their final report on the draft Toxicological Review of inorganic Arsenic (cancer).

(1) Taiwanese Water Consumption

There is very limited data available on water intake values for the arsenic exposed study population in southwest Taiwan. The U.S. EPA (1989) memo summarizes available information on water intake values. In the current (2010) draft of the Toxicological Review of inorganic arsenic (page 115, Table 5-1), U.S. EPA presents different water intake values and assumptions for Taiwanese men and women used in the arsenic cancer dose response modeling by U.S. EPA, NRC and others.

The NRC Panel report (2001; see pages 138-140) indicated that limited information was available for drinking water intake for Taiwanese populations when compared to the information available for U.S. populations. In the cancer dose response modeling, the NRC Panel report (2001) evaluated the impact of the variability in drinking water intake ratios (e.g., 1, 2.2, and 3) between U.S. and Taiwanese populations on Effective Dose estimates

(e.g., ED_{01}, LED_{01}). The NRC Panel report (2001) presented these results in Table 5-5 (see pages 196-198).

The impact of Taiwanese drinking water intake on dose response modeling is also discussed in the U.S. EPA *Arsenic Cancer Slope Factor Workgroup Issue Paper* (http://www.epa.gov/waterscience/criteria/arsenic/sab/ASIssues_SAB.pdf , dated July, 23, 2005). This paper captures the U.S. EPA's discussion regarding the NRC Panel report (2001) recommendations on cancer risk modeling parameters.

(2) Non-Water Arsenic Intake

U.S. EPA considered the arsenic in food sources (e.g., rice and yams) as the primary source of non-water (non-drinking water) arsenic intake. There is limited data available regarding the inorganic arsenic intake from food in Taiwanese populations. In particular the historical levels for the poor, largely subsistence based, rural populations studied are uncertain. The 2010 draft of the *Toxicological Review of Inorganic Arsenic (Cancer)* summarizes the available information on non-water intake (arsenic intake from non-drinking water sources) (see page 118 and 123 of the 2010 draft Toxicological Review). It is important to clarify that the non-water arsenic intake value corresponds to the arsenic amount from dietary sources (rice and yams, the dietary staples for the Taiwanese population in the endemic area) only. It does not include the arsenic intake value from water used for cooking rice or produce.

The NRC Panel report (1999) discussed available information on inorganic arsenic in Taiwanese food sources (see page 51 of the 1999 report). Neither of the NRC Panel reports (NRC, 1999; 2001) differentiated the background arsenic intake values in endemic areas versus intake values for Southwest Taiwan.

The following excerpted text is from the NRC Panel report (2001) and discusses background arsenic intake assumed for the Taiwanese population (see page 196 of the NRC, 2001 report -third paragraph, please note the bracketed insert in blue text was inserted by EPA to provide context http://nap.edu/openbook.php?record=10194&page=196)

> "The subcommittee addressed the issue of background arsenic in food by adding a constant concentration of arsenic to the exposure rates for all individuals in the study villages [i.e., the arsenic exposed population, not the reference population]. The assumed background rate in food was 30 µg/day (corresponding to 0.6 µg/kg/day, assuming a 50-kg weight for a Taiwanese person). The impact on the ED estimates by adding this amount was relatively small (approximately a 1% increase in ED estimates)."

In Section 5.3.5 (see pages 123 - 124) of the 2010 draft Toxicological Review of inorganic Arsenic (iAs; cancer) EPA concludes that 10 µg/day is a reasonable value for non-water arsenic intake for the southwest Taiwanese population and for the nationwide

Taiwanese reference populations, based on available information (U.S. EPA, 1989, and Schoof et al. 1998 for Taiwanese populations). The non-water intake value of 10 µg/day used in the current 2010 EPA modeling is greater than in the previous EPA analysis. In the previous arsenic risk assessment (U.S. EPA, 1988), U.S. EPA used 2 µg/day for background arsenic exposure from food sources. In the draft *Toxicological Review of Ingested Inorganic Arsenic* (U.S. EPA 2005, page 37), it was noted that the NRC (2001) used a series of assumptions for conducting the dose-response assessment, one of which was to utilize a background rate in food intake of 30 µg/day, assuming a 50 kg weight for a Taiwanese person (which was used in the EPA modeling, page 63 of US. EPA, 2005). It should be noted that using more than 10 µg/day as the assumed non-water arsenic intake for reference populations in the current arsenic cancer modeling increased the estimated cancer risks as reported in Table 5-10, 5-11 and Figure 5-2 (pages 139-140) of the draft toxicological review (See discussion in Item (6) below). The exposed population when modeled alone, was not sensitive (≤ 20% change) to increased non-water arsenic intake up to 200 µg/day. The sensitivity analysis demonstrated robustness when the exposed population was analyzed alone.

The dietary intake of arsenic for dose response modeling is also discussed in pages 19-21 of the *Arsenic Cancer Slope Factor Workgroup Issue Paper* (U.S. EPA, 2005) based on evaluation of the NRC Panel report (2001) recommendations on cancer risk modeling parameters.

(3) Southwest Taiwanese well arsenic concentrations

The following tables from the NRC Panel Report (1999), list the arsenic concentrations in wells from 42 endemic villages of southwest Taiwan (from six townships, see pages 308-309 of the NRC Panel Report, 1999).

Table A-10-1 Internal Cancer Data from Arsenic-Exposure Studies Conducted in Taiwan Region Endemic to Blackfoot Disease[a]

http://www.nap.edu/openbook.php?record_id=6444&page=309

	No. of			Person-Years		Bladder		Liver		Lung	
Village	Wells	Arsenic Concentration, ppm	Median	M	F	M	F	M	F	M	F
3-H	1	0.010	0.010	4,159	4,043	1	6	3	1	3	5
2-1	1	0.011	0.011	3,529	3,194	0	0	0	0	0	1
0-G	5	0.010, 0.010, 0.030, 0.259, 0.770	0.030	5,388	4,861	3	2	3	3	4	5
3-5	1	0.032	0.032	7,851	7,033	3	3	5	2	6	2
3-N	1	0.032	0.032	2,689	2,392	4	3	1	1	3	1
4-7	1	0.042	0.042	10,629	10,227	0	0	4	0	0	0
6-A	1	0.045	0.045	7,716	6,820	0	0	1	1	0	0
0-J	2	0.020, 0.080	0.050	6,501	5,888	1	0	2	2	0	0
3-L	2	0.053, 0.058	0.056	6,238	5,094	3	4	3	0	5	7
4-D	1	0.060	0.060	10,107	9,227	1	2	1	1	1	2
3-P	1	0.065	0.065	6,574	5,927	0	0	3	0	2	5
6-C	1	0.073	0.073	12,767	11,937	0	1	2	0	2	0
4-8	1	0.080	0.080	11,307	10,332	1	0	3	1	2	2
0-0	1	0.100	0.100	6,895	6,392	0	0	2	2	3	1
O-E	5	0.010, 0.085, 0.110, 0.288, 0.686	0.110	5,753	5,310	6	3	3	1	4	5
0-I	7	0.020, 0.050, 0.110, 0.110, 0.190, 0.580, 0.590	0.110	4,249	3,833	0	2	1	3	3	2
4-N	2	0.073, 0.172	0.123	4,709	4,291	0	0	3	1	1	2
4-J	1	0.126	0.126	6,508	6,026	0	1	6	1	2	2
2-D	1	0.256	0.256	9,702	8,869	0	2	2	1	7	1
0-D	1	0.256	0.256	3,872	3,412	1	3	2	3	5	2
3-Q	6	0.148, 0.198, 0.242, 0.276, 0.291, 0.458	0.259	5,580	5,079	2	0	4	2	5	4
4-M	1	0.307	0.307	2,953	2,758	1	0	0	0	2	3
6-6	1	0.307	0.307	5,364	4,505	3	0	3	1	4	1
4-E	2	0.340, 0.360	0.350	3,942	3,586	0	0	1	0	0	1
4-L	2	0.310, 0.485	0.398	3,069	2,723	1	1	1	0	0	1

Table A-10-1 (Continued) Internal Cancer Data from Arsenic-Exposure Studies Conducted in Taiwan Region Endemic to Blackfoot Disease[a]

http://www.nap.edu/openbook.php?record_id=6444&page=309

	No. of			Person-Years		Bladder		Liver		Lung	
Village	Wells	Arsenic Concentration, ppm	Median	M	F	M	F	M	F	M	F
4-F	11	0.120, 0.170, 0.229,0.260, 0.260, 0.406,0.469, 0.485, 0.595, 0.779, 0.819	0.406	4,482	3,886	2	3	1	0	5	1
3-1	1	0.448	0.448	4,551	4,259	2	3	5	1	4	3
5-G	1	0.467	0.467	3,179	5,298	7	5	2	3	7	1
4-P	1	0.504	0.504	5,843	5,397	1	0	1	1	1	1
0-H	5	0.050, 0.394, 0.520, 0.610,1.752	0.520	4,390	4,313	3	2	4	0	4	5
4-1	47	0.020, 0.020, 0.030, 0.090, 0.100, 0.110, 0.120, 0.5200.120, 0.160, 0.190, 0.230, 0.240, 0.250, 0.270, 0.270, 0.290, 0.290, 0.350, 0.370, 0.410, 0.430, 0.450, 0.510, 0.520, 0.540, 0.560, 0.660, 0.700, 0.730, 0.740, 0.760, 0.760, 0.760, 0.780, 0.810, 0.810, 0.840, 0.840, 0.850, 0.850, 0.850, 0.870, 0.880, 0.900, 0.930, 0.940, 0.970	0.520	4,870	4,432	2	2	1	0	3	5
3-J	2	0.529, 0.529	0.529	8,454	8,689	4	8	3	1	6	5
3-S	2	0.480, 0.595	0.538	4,287	3,667	4	3	7	0	8	4
3-9	1	0.544	0.544	3,655	3,413	0	1	1	1	1	0
2-2	10	0.560, 0.580, 0.580, 0.590, 0.597, 0.600, 0.618, 0.620, 0.650, 0.704	0.599	9,059	7,977	2	2	9	5	8	5
4-G	2	0.620, 0.680	0.650	2,425	2,108	2	0	0	0	2	2
5-4	2	0.630, 0.735	0.683	3,155	2,983	1	1	2	1	5	2
2-M	2	0.435, 0.950	0.693	11,123	11,263	9	9	6	4	14	4
0-F	5	0.415, 0.660, 0.694, 0.720, 0.749	0.694	7,010	5,720	5	1	8	3	2	9
3-R	5	0.397, 0.440, 0.698, 0.750,1.010	0.698	4,310	3,576	3	6	3	2	6	7
3-M	4	0.221, 0.329, 1.105,1.411	0.717	5,815	4,877	0	1	2	0	0	0
2-N	3	0.560, 0.934, 0.960	0.934	8,341	8,342	7	10	8	2	4	4

aData from Wu et al. 1989; Chen et al. 1992.

(4) Availability of U.S. EPA (1989) memo (i.e., the Abernathy 1989 memo)

The U.S. EPA (1989) memo is attached along with this document. The U.S. EPA (1989) memo was provided to the SAB Work Group during the meeting.

(5) Geographic Locations of the Reference Populations

In the 2010 draft of the *Toxicological Review for Inorganic Arsenic (cancer)*, U.S. EPA used the Southwest Taiwan population as a reference population in the baseline risk estimation from arsenic exposure in drinking water. This approach conforms to advice that EPA received from the NRC (2001) and the SAB (2007). To develop the sensitivity analyses of this issue suggested by the SAB (2007), U.S. EPA also included 'none' (i.e., no reference population) or 'all Taiwan' as reference populations in comparisons with baseline cancer risks. In the U.S. EPA *Arsenic Cancer Slope Factor Workgroup Issue Paper* (dated July, 23, 2005), the U.S. EPA included an external population for comparison in dose response modeling (Page 16).

The SAB Work Group requested clarification regarding the geographic locations of the reference populations. The geographical unit of Taiwan is in the following order with respect to the size of the area: Villages<Townships<Counties<Country (Taiwan). The following maps indicate the locations of the reference populations used in the dose response modeling.

(a) Tsai et al. (1999)

Tsai et al. (1999) is the first publication providing information on geographic locations for the southwest Taiwan or all Taiwan for reference populations. The southwest Taiwan populations refer to populations from townships in two nearby counties of an endemic area of southwest Taiwan. Based on the published figure, the Southwest Taiwan reference population comes from predominantly Tainan and Chiyai counties. (a more legible and detailed map for these counties is found in section 5 (c)).

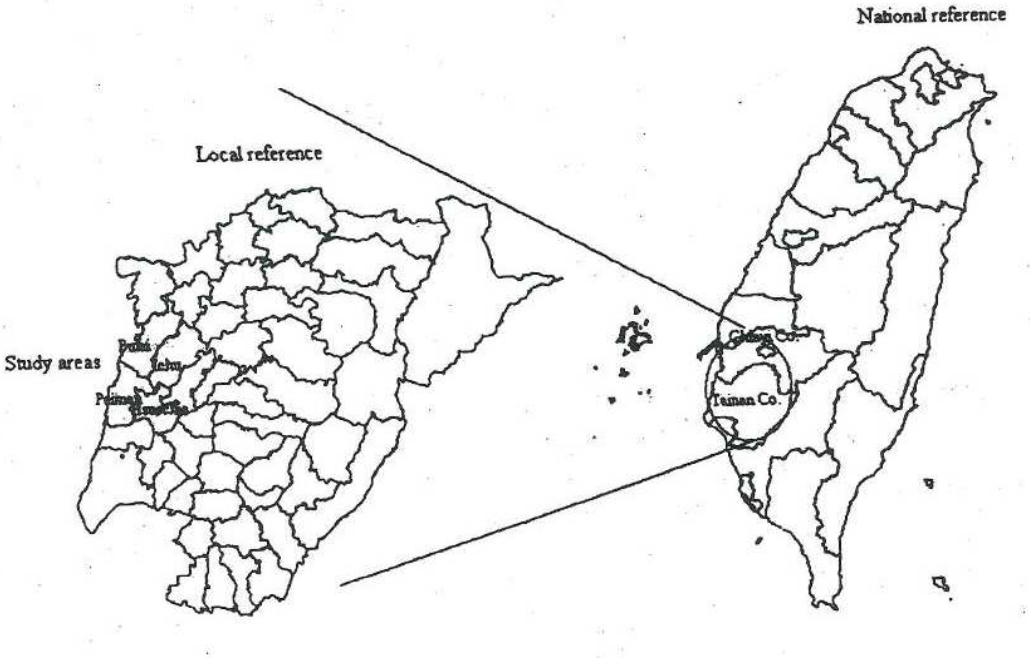


Figure 1 **Locations of study areas, local reference group, and national reference group. Tsai et al. May/June 1999 (Arch Environ Health 54(3):186-193.**

(b) Counties in Taiwan

The geographic locations of counties in Taiwan are provided below.

Taiwan counties

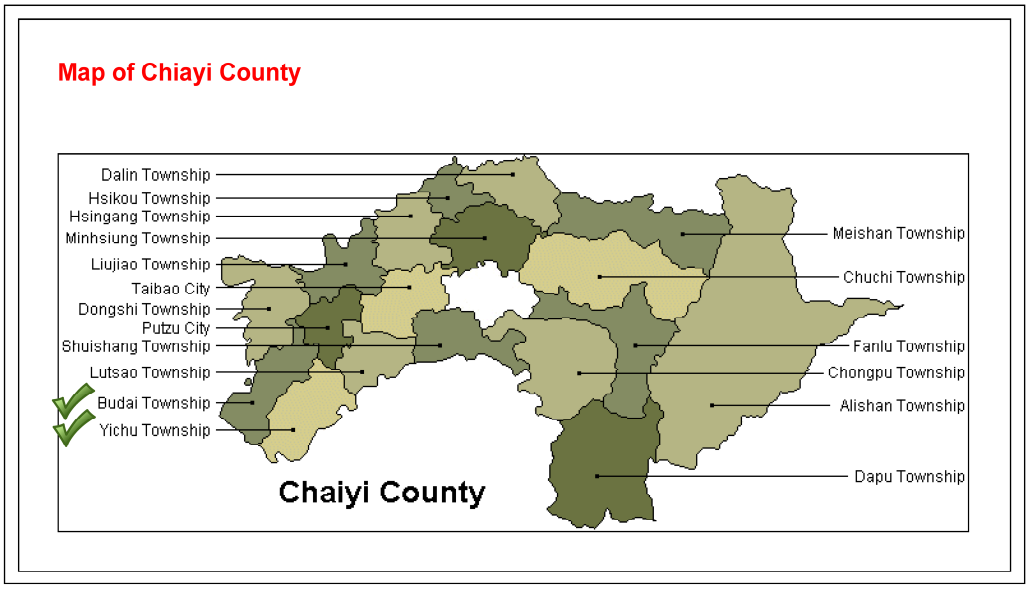
click on a name for a list of cities and districts

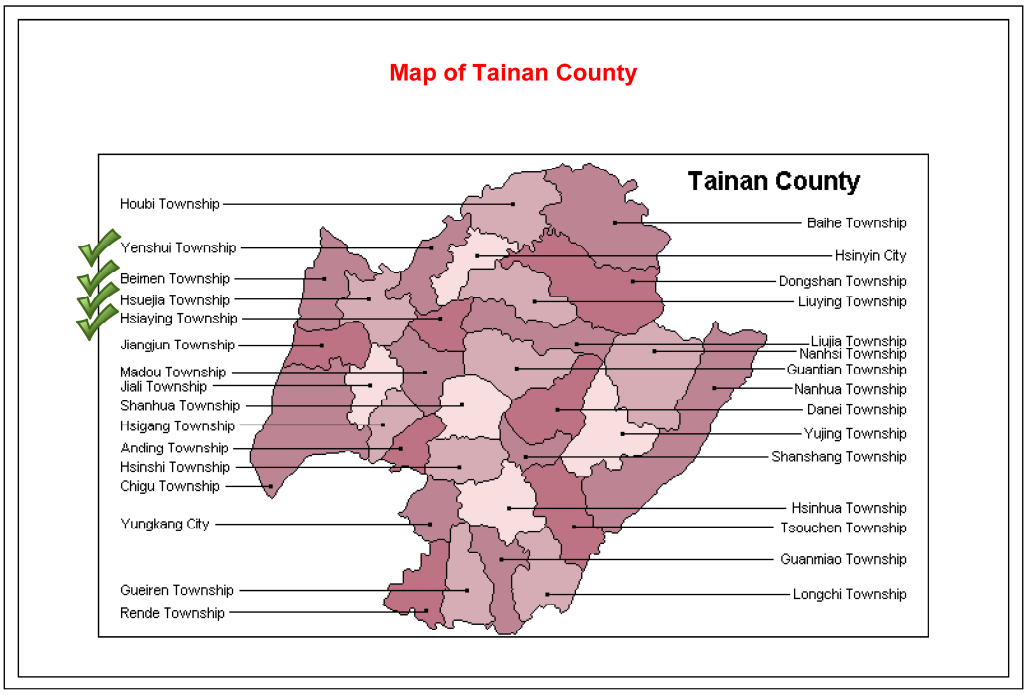
Chinese traditional		pinyin
彰化縣	Changhua	Zhanghua
嘉義縣	Chiayi	Jiayi
新竹縣	Hsinchu	Xinzhu
花蓮縣	Hualien	Hualian
宜蘭縣	Ilan	Yilan
高雄縣	Kaohsiung	Gaoxiong
苗栗縣	Miaoli	Miaoli
南投縣	Nantou	Nantou
澎湖縣	Penghu	Penghu
屏東縣	Pingtung	Pingdong
台中縣	Taichung	Taizhong
台南縣	Tainan	Tainan
台北縣	Taipei	Taibei
台東縣	Taitung	Taidong
桃園縣	Taoyuan	Taoyuan
雲林縣	Yunlin	Yunlin
高雄市	Kaohsiung City	Gaoxiong City
台北市	Taipei City	Taibei City

Source: http://www.romanization.com/cities/index.html

(c) Townships in Taiwan

The geographic locations of townships within Taiwan are indicated in the figures below. The six townships marked with a check mark are Blackfoot disease endemic areas. These townships reside in same two counties, Chiayi and Tainan. The Chiayi and Tainan counties served as the southwest Taiwan reference population.





Source: http://www.taiwan.com.au/Envtra/Geography/Maps/Chiayi02.html;
http://www.taiwan.com.au/Envtra/Geography/Maps/Tainan02.html

(d) Wu et al. (1989)

The following figure from the Wu et al. (1989) article (see page 1125) indicates the geographic locations of 42 villages from the Blackfoot disease endemic area of southwest Taiwan. These 42 villages are in following townships: Peimen, Hsuechia, Putai, and Ichu, Yensui and Hsiaying. Yensui and Hsiaying included 15 villages, with the remaining 27 villages coming from the other four townships. .

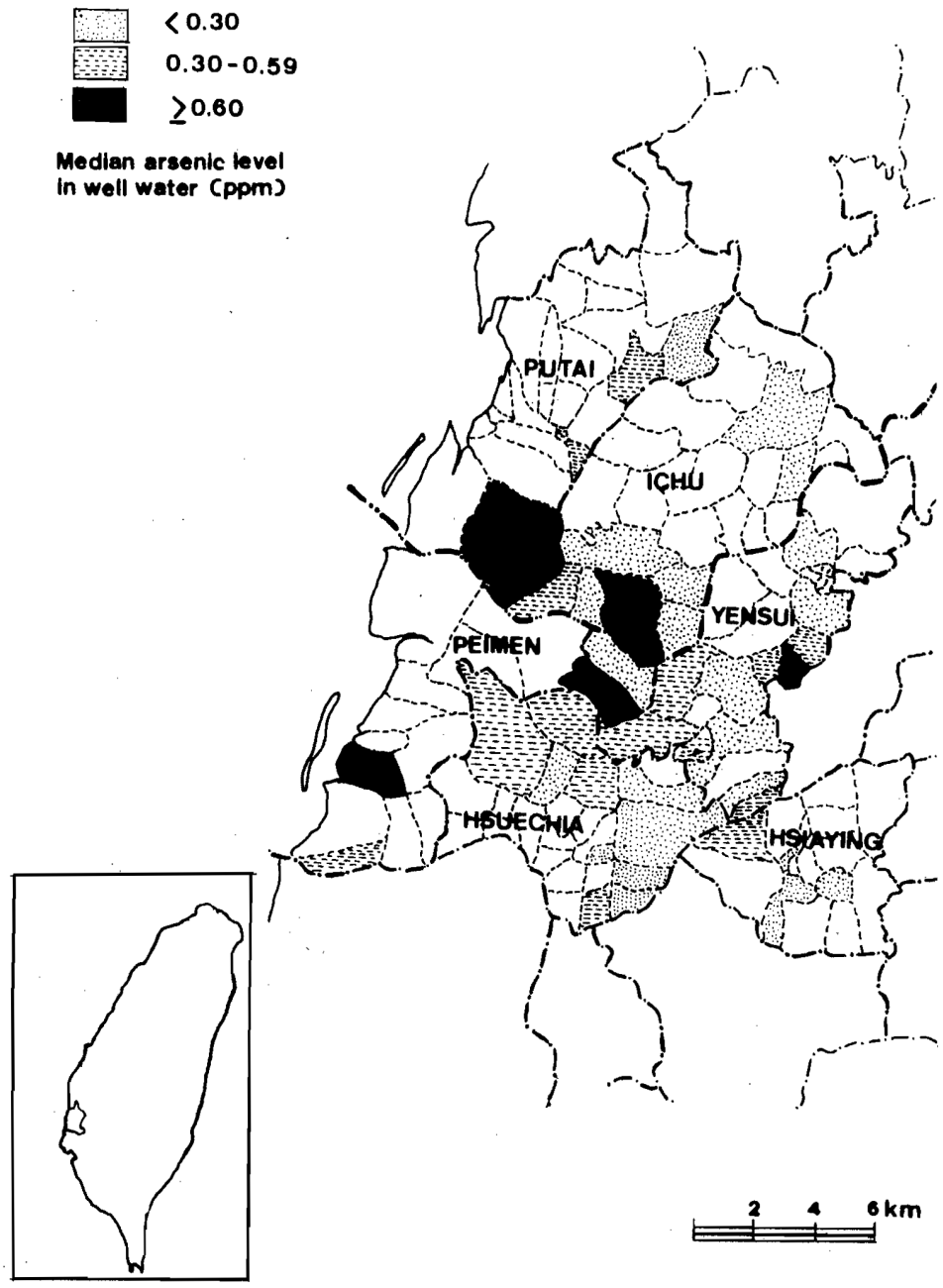


FIGURE 1. Geographic distribution of 42 studied villages in the endemic area of blackfoot disease in Taiwan, by median arsenic level of well water determined in 1964–1966.

(e) NRC, 2001

In describing the reference populations used in the Tsai et al., (1999) publication, the NRC Panel report (2001) stated the following (see page 36):

> "Observed mortality between 1971 and 1994 was compared with age and sex-specific expected mortality based on data from (1) a local reference group derived from two nearby counties, and (2) all of Taiwan. The local reference group was considered to be similar to the study group with respect to lifestyle factors; however, the drinking-water arsenic concentration of the local reference area was not stated."

The NRC Panel report (2001) recommended using a reference population. The following excerpt is from the NRC Panel report (2001) "Summary and Conclusions" Section (see page 207):

> "Although it can be argued that an external comparison group for dose-response analysis of the original Taiwanese data should not be used, the subcommittee believes that such arguments are outweighed by evidence in favor of using a comparison population. A recent paper by Tsai et al. (1999) decreases concerns about the potential role of confounding in using either the southwestern Taiwanese population or the entire Taiwanese population as an external comparison group."

The NRC Panel report (2001) discusses cancer risks estimated with and without the use of reference population from the previous NRC Panel report (1999) analysis (see pages 190 -193 of the NRC Panel report, 2001).

(f) SAB Report 2007

The previous SAB report (2007) concluded that the NRC (2001) recommendation to base risk assessments on a linear dose response that includes the southwestern Taiwan population as a comparison group seems the most appropriate approach. The SAB report (2007) also recommended conducting a sensitivity analyses based upon three options for the reference population (all Taiwan, southwest Taiwan, and none) for the dose response modeling. The following statements are excerpted from page 9 and 49 of the SAB report (2007):

> **Page 9** (SAB, 2007) *Charge Question D2 - Summary Response*
> http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=494507
> The Panel concluded that:
>
> i) Inorganic arsenic has the potential for a highly complex mode of action.
>
> ii) Until more is learned about the complex PK and PD properties of iAs and its metabolites there is not sufficient justification for the choice of a specific nonlinear form of the dose-response relationship.

iii) The NRC (2001) recommendation to base risk assessments on a linear dose response model that includes the Southwestern Taiwan population as a comparison group seems the most appropriate approach.

iv) The Panel also recommends that EPA perform a sensitivity analysis of the Taiwanese data with different exposure metrics, with the subgroup of villages with more than one well measurement, and using a multiplicative model that includes a quadratic term for dose.

Page 49 (SAB, 2007)

Following the series of checks and corrections to the model listed above, the Panel encourages the Agency to extend its testing of the model sensitivity to alternative models forms and model assumptions. Specific areas where the Panel felt additional sensitivity testing is warranted include:

a) A Monte Carlo analysis in which the individual well concentrations for 22 villages with multiple wells are taken into account. The Panel recognizes the difficulties with this approach including the issue of how to allocate cases to wells within villages.

b) MCCancerFit.xls:
   a. A test of the sensitivity of the model to the choice of the reference population (SW Taiwan).
   b. A test of the sensitivity of model results to the assumption that the reference population has 0 intake of arsenic via food.
   c. A contrast of results for the linear dose model employed in this program to alternative hazard models that are multiplicative and nonlinear in form. For example, the following multiplicative, quadratic model is one of several that NRC (2001) found to have 'best fit to the data' based on the Akaike Information Criterion (AIC):

$$\lambda_{,} = \exp(a + a_2 \cdot age + a_3 \cdot age) \cdot \exp(\beta + \beta \cdot dose + \beta \cdot dose)$$

(6) Increased female bladder cancer results

EPA's sensitivity analysis indicated that the arsenic unit risk estimate for female bladder cancer is sensitive to the estimated "non-water arsenic" intake (which applies to estimated exposure for both the reference and the exposed populations). Estimated female bladder cancer risks increase when higher levels of this non-water arsenic exposure are assumed (i.e., 267% [non-water arsenic intake = 50 μg/day (reference and exposed

populations)]). This sensitivity is specific to the assumed arsenic intake for the reference population as other analyses (see Tables 5-10 & 5-11) demonstrate that increasing the “non-water arsenic” for the exposed population alone has little influence on the estimated risks.

The mathematical behavior of the model results can be understood in the following manner: When arsenic intake for the reference and exposed populations is increased, the model parameters change so as to predict occurrence of a larger proportion of the female bladder cancer mortality in the reference and exposed populations attributable to the background arsenic exposure. Therefore, the background-cancer mortality estimate would decrease in the absence of any arsenic exposure. This also implies that the relative cancer risks for the arsenic exposed population as compared to this background rate increase. Note that the Taiwanese mortality data was converted to cancer incidence for the U.S. populations for the purposes of estimating the oral cancer slope factor. Finally this also leads to sensitivity of the final cancer potency estimate as a relative risk calculation is used to estimate risks for cancer incidence due to arsenic exposures in the US population. While in principle this mathematical behavior would be relevant to findings for all cancer sites, in practice; risk estimates for other sites are much less sensitive to the background arsenic intake assumption compared to the female bladder cancer risk result. This is largely due to the fact that (prior to any modeling) the observed relative risks for the arsenic-exposed population for female bladder cancer are higher than for the other cancer sites.