Arsenic Exposure and Potential Health Impact in the Pacific Basin Countries

Kathleen M McCarty, ScD, MPH
Assistant Professor
Yale University School of Medicine
Department of Epidemiology & Public Health
Division of Environmental Health Sciences

Pacific Basin Rim Conference
Perth Australia
November 22, 2009

Outline

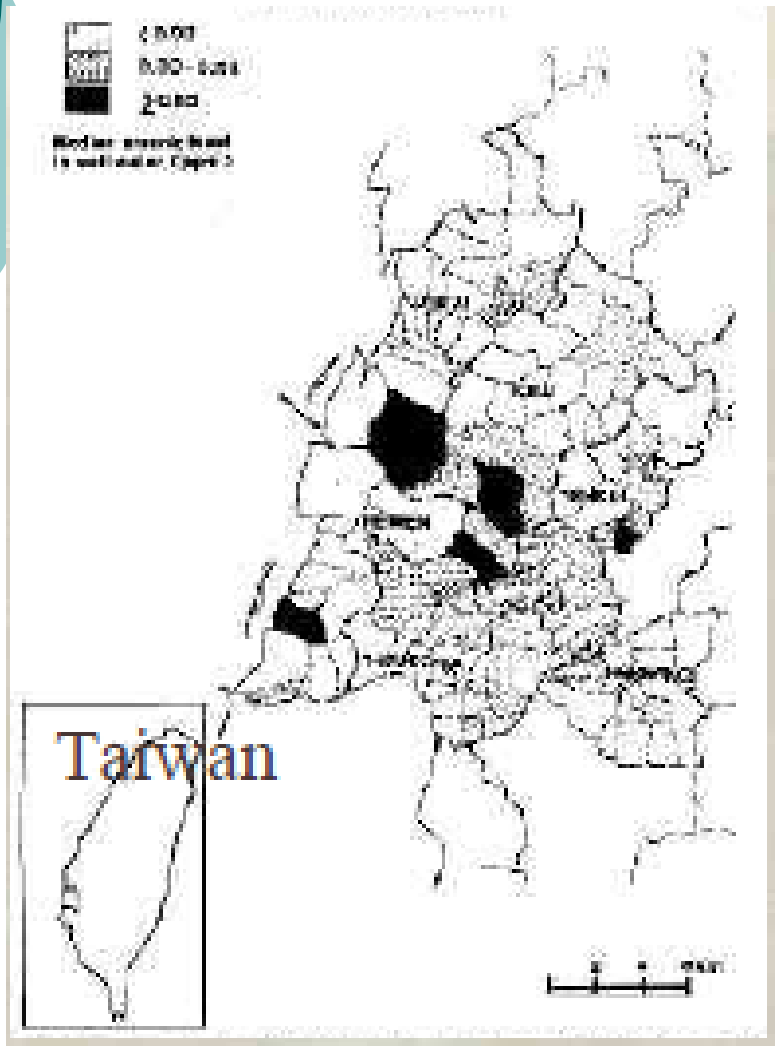
- Arsenic…what we know so far
- SE Asian Countries
- Why do we see different disease endpoints and effects at varying exposures?
- Areas for future study

Arsenic Impact on Human Health

Inorganic arsenic exposure has been associated with:

- Cancer Outcomes:
  - Lung
  - Skin
  - Bladder
  - Kidney cancer
  - Prostate
- Non-Cancer Outcomes:
  - Hypertension
  - Diabetes
  - Cardiovascular changes
  - Cognitive function
  - Skin lesions
  - Immune Function

Taiwan and Blackfoot Disease



- The blackfoot disease (BFD), which was endemic peripheral vascular disease in southwestern Taiwan before the 1990s, has known to be caused by drinking arsenic-contaminated groundwater.
- Arsenic is as the most important determinant BFD, several compounds are found in the high arsenic well water, including ergotamine, organic chloride, and fluorescent humic substances.
- Trace elements: molybdenum, mercury, copper, and cadmium, were reported to be higher in the serum and/or urine of BFD patients and in the groundwater.

Blackfoot Disease

- Etiology of BFD is rather complicated and remains unclear up to present.
- Symptoms for the patients from the southwestern coast (SW) of Taiwan (Chia-Nan plain) were significantly different from those in the northeastern (NE) coast of Taiwan (Ilan plain)

Blackfoot Disease

- **SW Coast symptoms**: **characterized particularly by BFD**, skin diseases (e.g., hyperkeratosis, skin cancer, etc.) and internal cancers (e.g., lung, bladder, prostate, etc.) that were caused by arsenic and lesser amounts of fluorescent humic substances in the groundwater

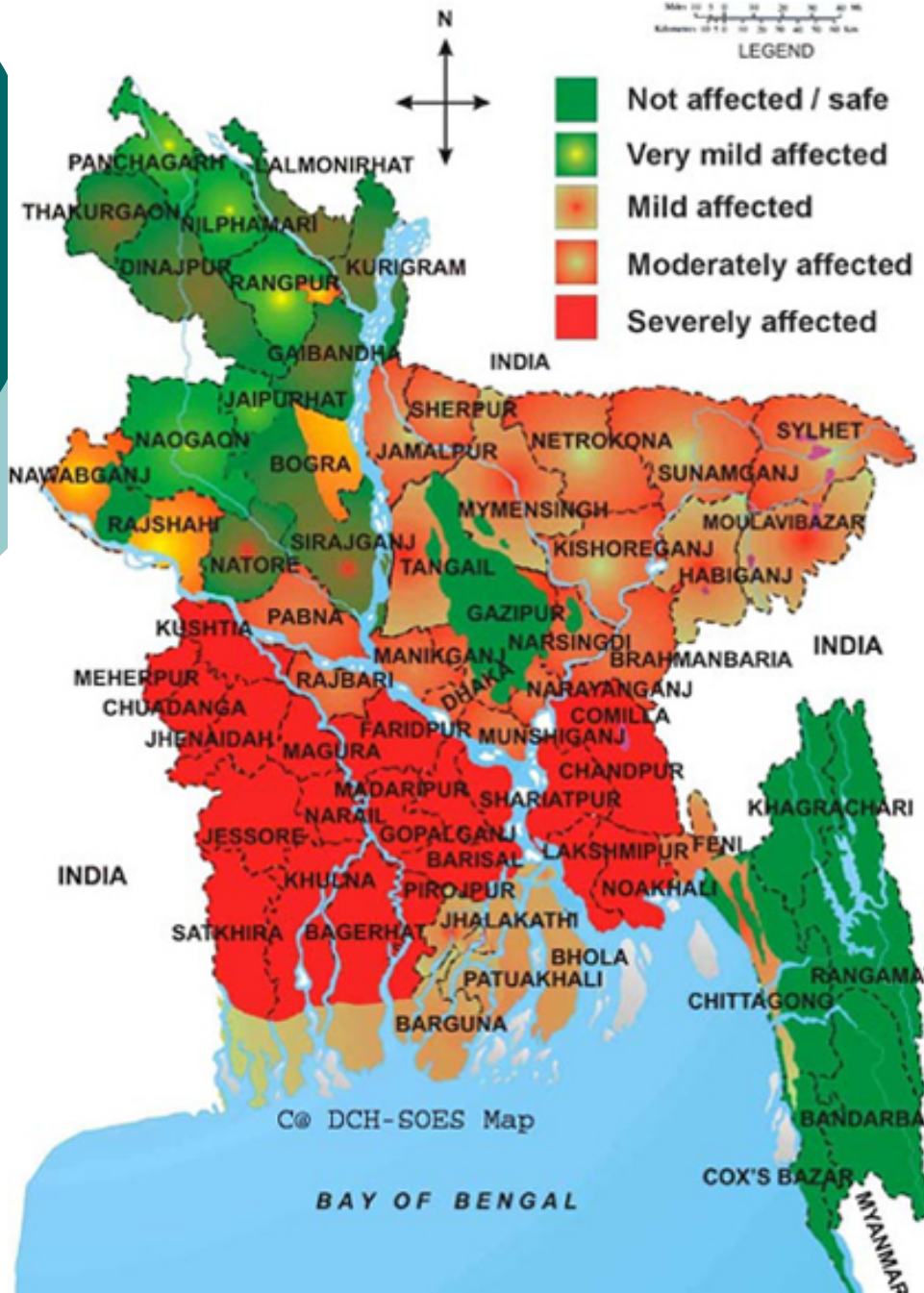
- **NE Coast Symptoms**: characterized particularly by skin diseases and internal cancers but **NO BFD** that were caused by arsenic and considerable amounts of fluorescent humic substances in the groundwater.

Bangladesh

- The arsenic exposure in drinking water in Bangladesh is a public health emergency
- "Largest mass poisoning of a population in history"

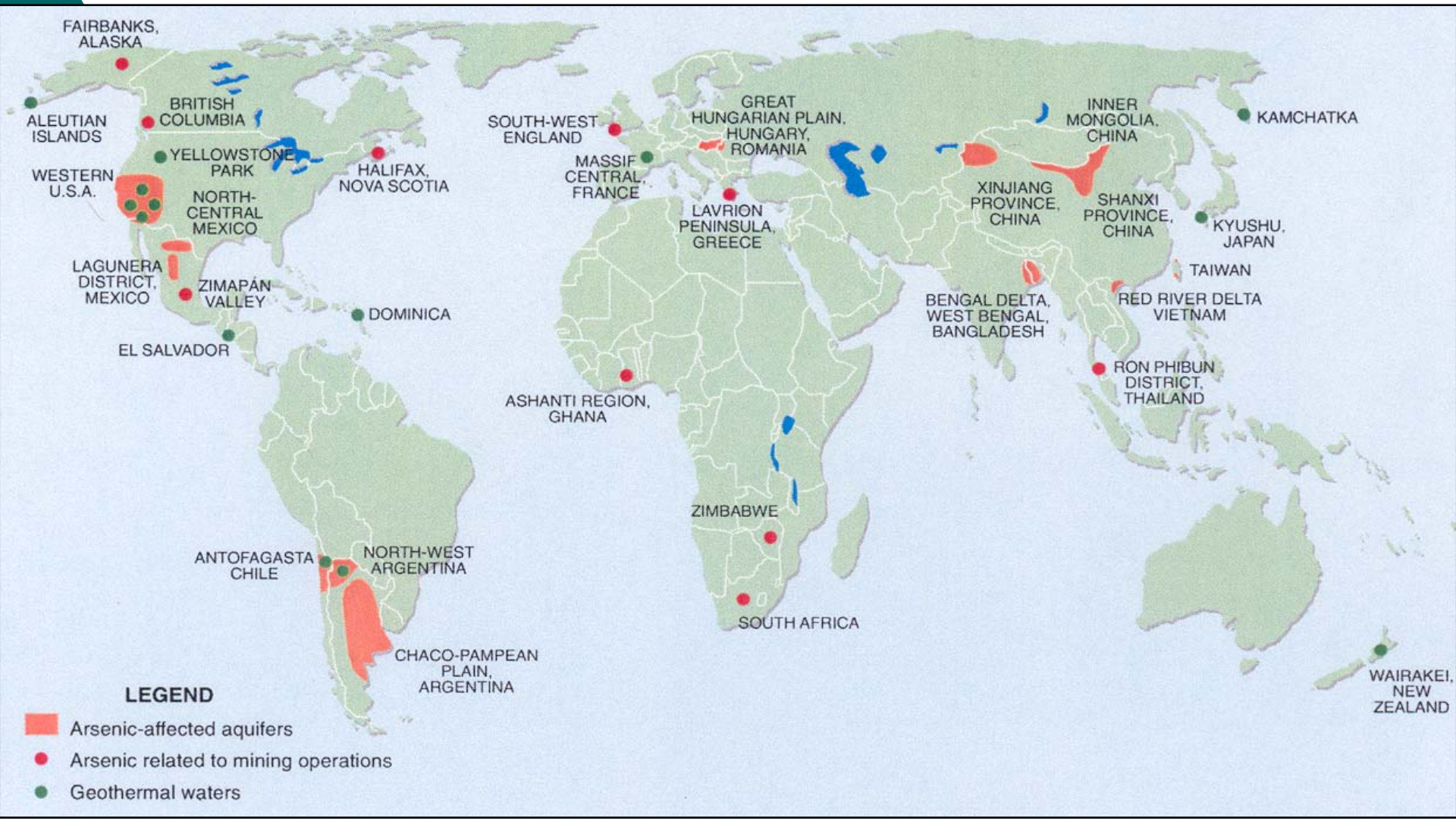
(*World Health Organization,2000*)

- Levels of arsenic in the drinking water put over 100 million people at increased risk



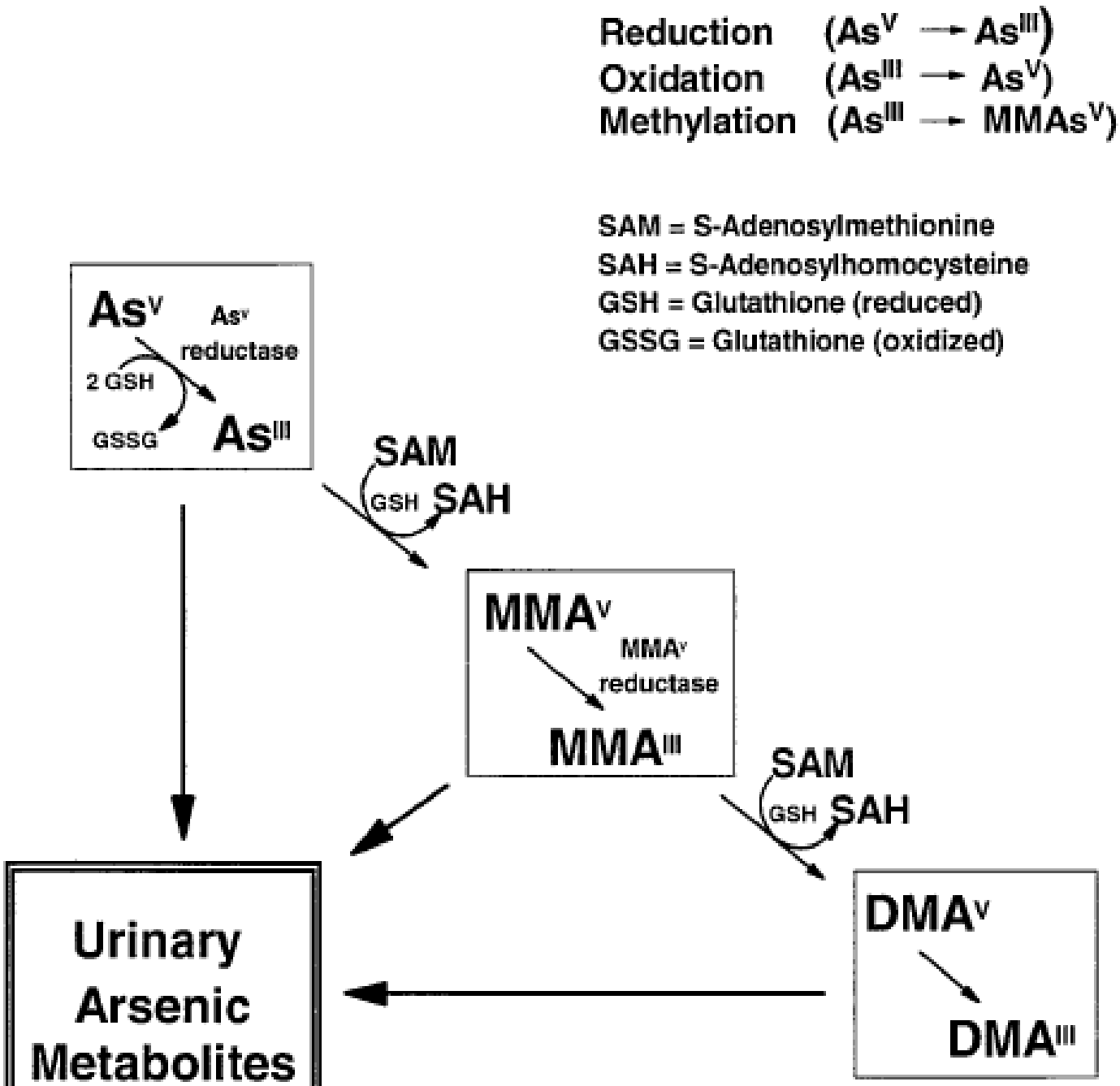
Photograph courtesy of Harvard Arsenic Project
http://phys4.harvard.edu/%7Ewilson/arsenic_project_pictures2_files/arsenic_project_sufferer_picture35.jpg

Global Contamination of Groundwater

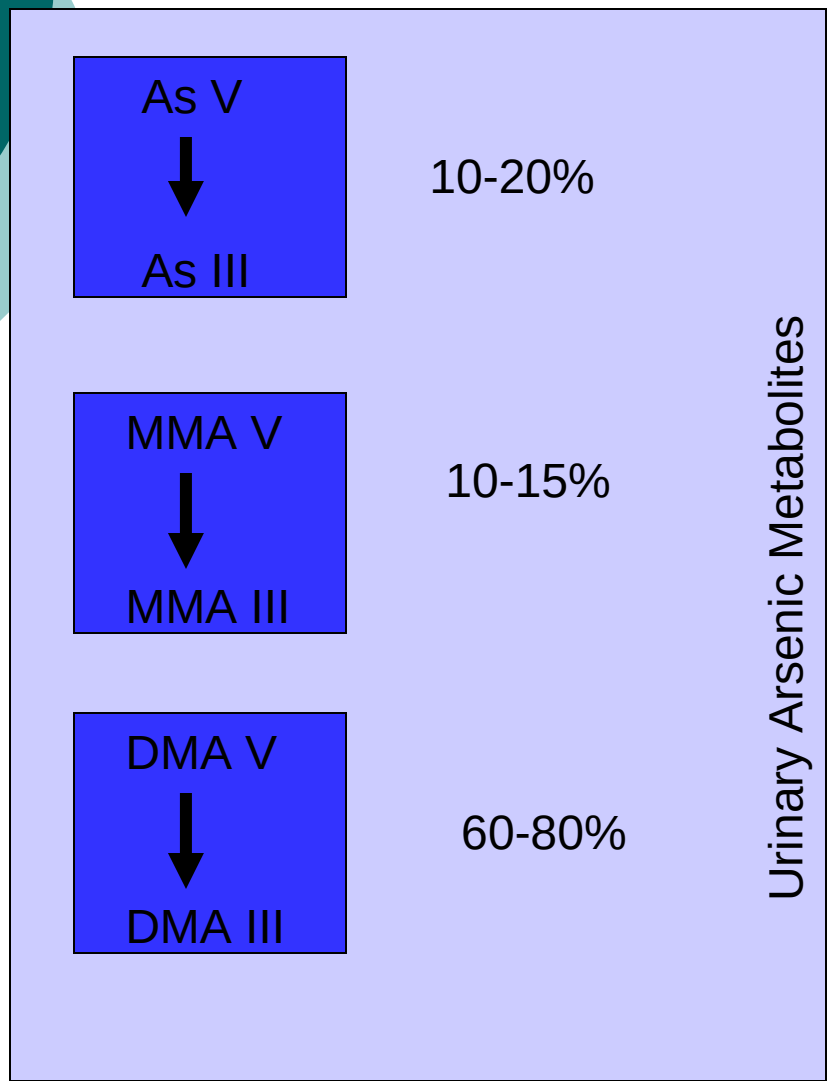


Courtesy of British Geological Society (http://www.bgs.ac.uk/arsenic/Bangladesh/Reports/ChapWorldReview.pdf)

ARSENIC METABOLISM



Urinary Arsenic Methylation



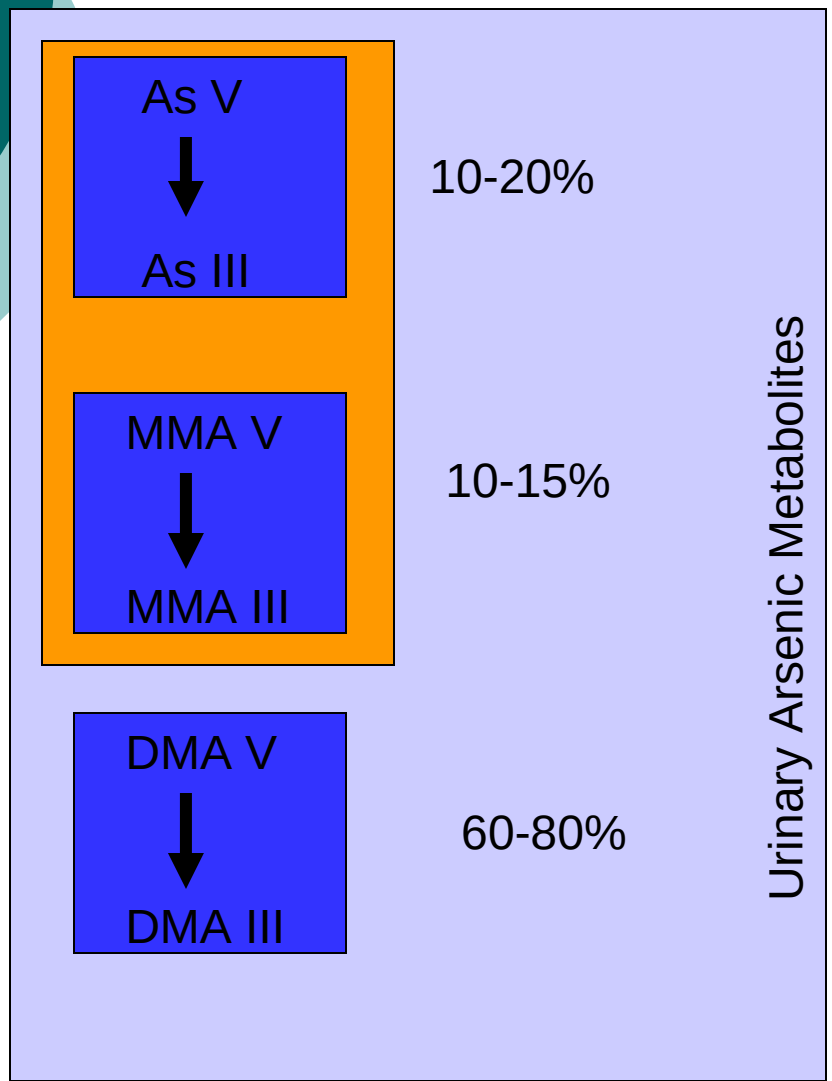
- Higher primary methylation ratios (MMA/In As) have been associated with skin cancer cases, skin lesion cases, and bladder cancer.

  (Hsueh et a, 1997; Yu et al 2000; Chen et al, 2003; Chen et al 2003, McCarty et al, 2006)

- Decreased secondary methylation ratios (DMA/MMA) have been associated with an increase in skin cancer and in bladder cancer with elevated arsenic exposure.

(Hsueh et al, 1997; Yu et al, 2000; Chen et al, 2003; Chen et al 2003)

Urinary Arsenic Methylation



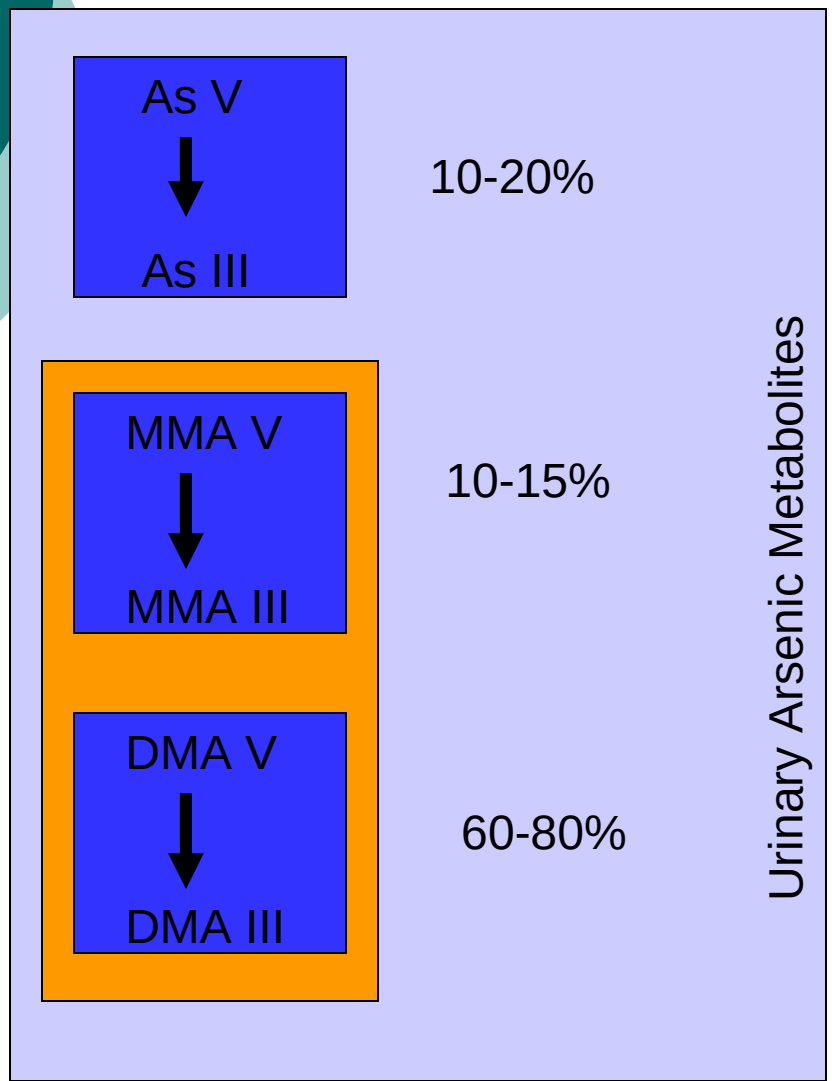
- Higher **primary methylation ratios** (MMA/InAs) have been associated with skin cancer cases,skin lesion cases and bladder cancer.

  (Hsueh et a, 1997; Yu et al 2000; Chen et al, 2003; Chen et al 2003, McCarty et al, 2006)

- Decreased secondary methylation ratios (DMA/MMA) have been associated with an increase in skin cancer and in bladder cancer with elevated arsenic exposure.

  (Hsueh et al, 1997; Yu et al, 2000; Chen et al, 2003; Chen et al 2003)

Urinary Arsenic Methylation



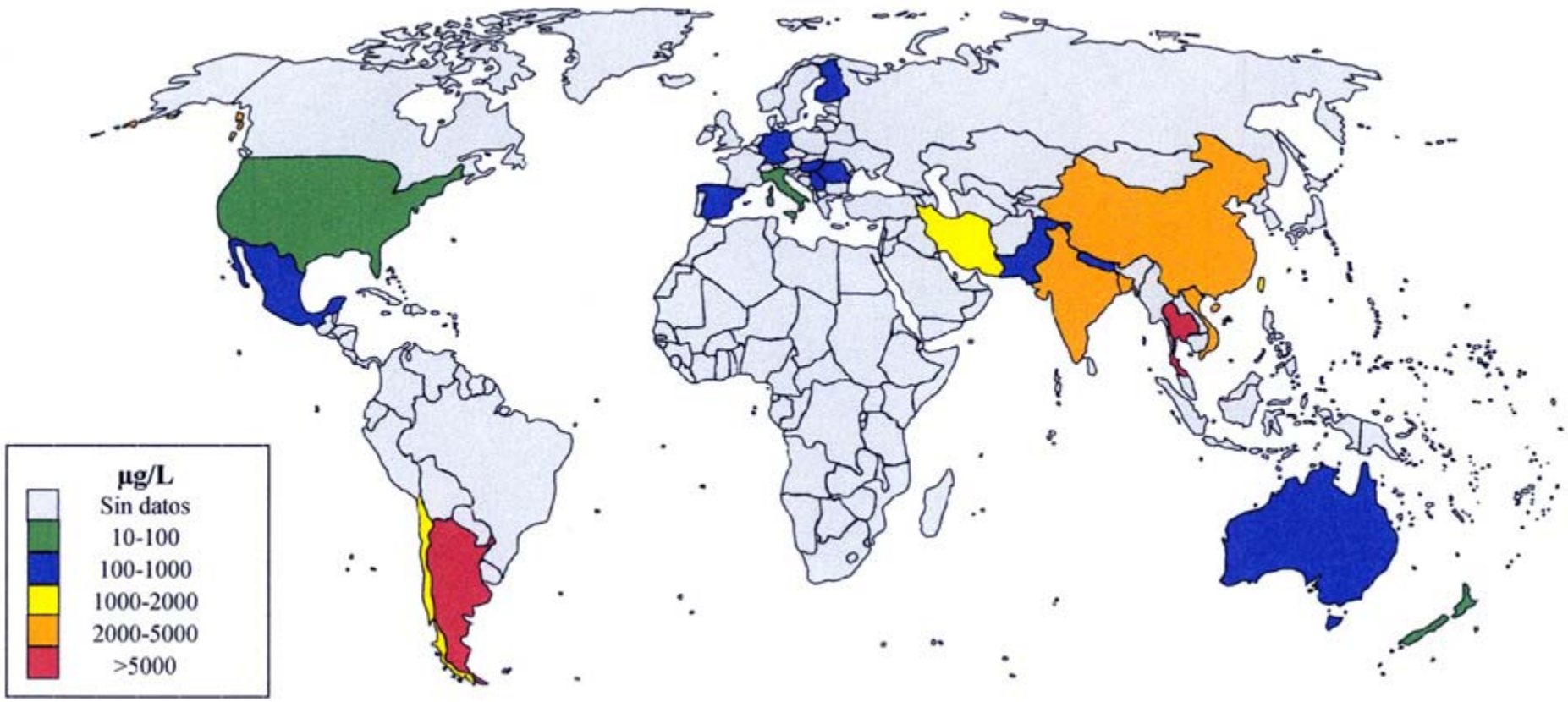
- Higher primary methylation ratios (MMA/In As) have been associated with skin cancer cases, skin lesion cases, and bladder cancer.

  (Hsueh et a, 1997; Yu et al 2000; Chen et al, 2003; Chen et al 2003; McCarty et al 2006)

- Decreased **secondary methylation ratios (DMA/MMA)** have been associated with an increase in skin cancer and in bladder cancer with elevated arsenic exposure.

  (Hsueh et al, 1997; Yu et al, 2000; Chen et al, 2003; Chen et al 2003)

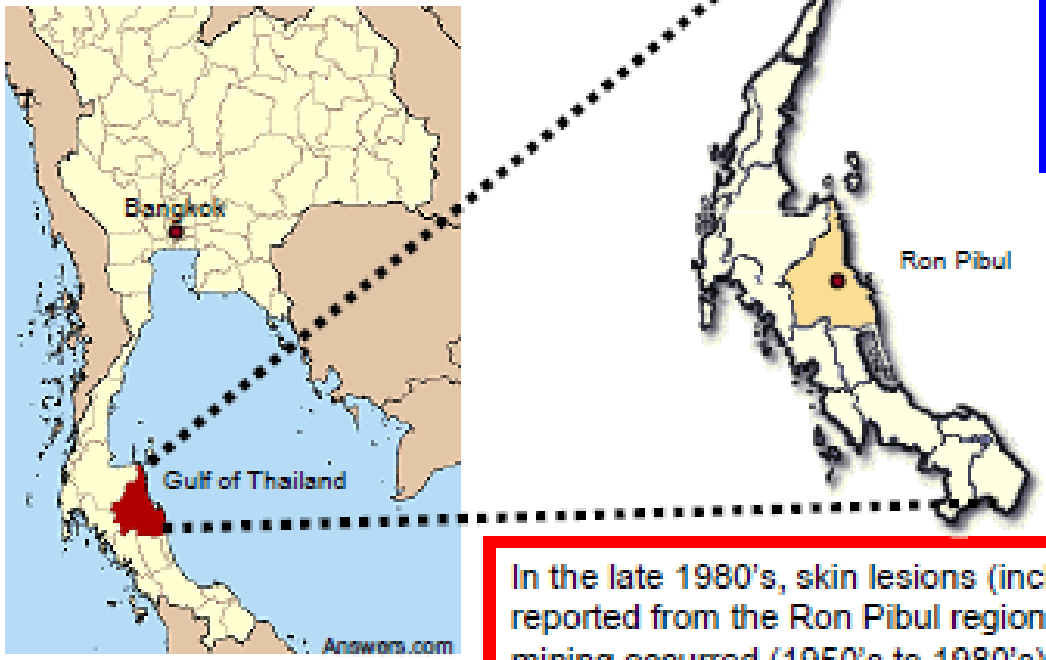
World Concentrations of Arsenic in Drinking Water



Map Courtesy of NIEHS

Study location: Ron Pibul District in Thailand: Tin Mining Contaminated Ground Water

Nakhon Si Thammarat Province



Arsenic exposure exceeds WHO limit

up to 100X WHO limit

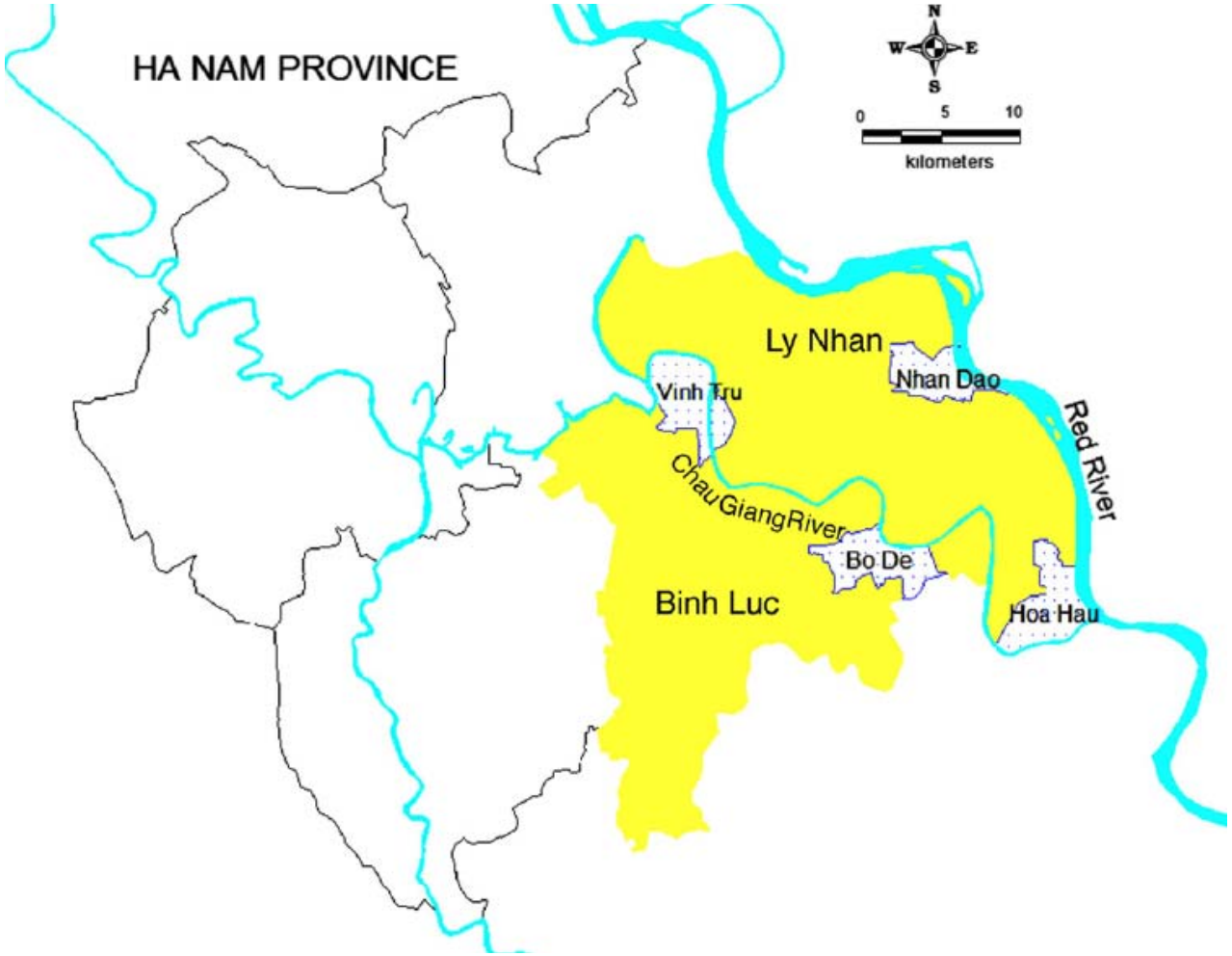
In the late 1980's, skin lesions (including skin cancer) were reported from the Ron Pibul region of Thailand where tin mining occurred (1950's to 1980's)

Concentration of arsenic in water samples and nails in mothers and newborns residing in Ron Pibul District, Thailand

Groups	Total As in Nails (µg/g)		Drinking water	Non-drinking water
	Toenails	Fingernails	(µg/l)	(µg/l)
Mother	6.36 ± 2.86	2.87 ± 1.39	2.54 ± 0.42	143.46 ± 64.18
	1.62(0.32-68.63)	0.67 (0.16-29.8)	1.29 (0.69-5.85)	18.60 (4.91-1,475)
	n=24	n=24	n=24	n=24
Newborn	1.79 ± 0.73	2.52 ± 0.93	NA	NA
	0.68 (nd-7.63)	1.15 (nd-19.85)	NA	NA
	n=14	n=22		

Values are expressed as Mean±SE on the first line and Median (mininum - maximum) on the second line

Vietnam


HA NAM PROVINCE
N
W
E
S
0
5
10
kilometers
Ly Nhan
Nhan Dao
Vinh Tru
Red River
ChauGiangRiver
Bo De
Binh Luc
Hoa Hau

Vietnam

Location	*n*	Mean	Min	Max	Median	References
Red River Delta						
Cat Que Commune, Ha Tay Province	13	209	132	344	194	This study
Vinh Tru Commune, Ha Nam Province	15	163	1.8	486	153	This study
Van Duc Commune, Gia Lam Province	11	10.8	<0.1	38.2	5.0	Agusa et al. (2006)
Van Phuc Commune, Thanh Tri Province	14	44.0	<0.1	330	1.5	Agusa et al. (2006)
Dong Anh Province	48	31	<1	220		Berg et al. (2001)
Gia Lam Province	55	127	2	3050		Berg et al. (2001)
Thanh Tri Province	45	432	9	3010		Berg et al. (2001)
Tu Liem Province	48	67	1	230		Berg et al. (2001)
Luong Yen, Hanoi	6	22.8				Nga et al. (2003)
Yen Phu, Hanoi	7	40.5				Nga et al. (2003)
Mai Dich, Hanoi	3	1.1				Nga et al. (2003)
Ngoc Ha, Hanoi	3	1.6				Nga et al. (2003)
Ngoc Si Lien, Hanoi	3	1.4				Nga et al. (2003)
Phap Van, Hanoi	5	67.3				Nga et al. (2003)
Tuong Mai, Hanoi	4	44.5				Nga et al. (2003)
Ha Dinh, Hanoi	5	92.6				Nga et al. (2003)
Red River Delta	83	140	1.3	460		Trang et al. (2005)
Mekong River Delta						
An Giang Province	24	5.4	<0.1	71.2		Minh et al. (2005)
Can Tho Province	42	3.7	<0.1	23		Minh et al. (2005)
Don Thap Province	12	96.5	<0.1	411		Minh et al. (2005)
Soc Trang Province	2	6.0	<0.1	12		Minh et al. (2005)
Ben Tre Province	2	66.6	47.1	86.1		Minh et al. (2005)
Ho Chi Minh	10	5.5	<0.1	32.7		Minh et al. (2005)
Long An Province	6	13.5	<0.1	30.4		Minh et al. (2005)
Tien Giang Province	10	7.7	<0.1	29.5		Minh et al. (2005)
Vinh Long Province	10	1.5	<0.1	4.54		Minh et al. (2005)
Mekong River Delta	111	39	<1	850		Trang et al. (2005)

Agusa et al. 2009 Environmental Pollution

Concentration of arsenic in water samples and nails of pregnant women residing in Vanxa Commune, Kimbang District, Hanna Province, Vietnam

	As in nails (µg/g)[1]	As in ground water (µg/l)[2]	
		before[3]	after[3]
n	20	19	19
Mean ± SE	0.97 ± 0.09	116.47 ± 13.77	42.11 ± 25.51
Median	0.930	150	50
Range	0.33-1.82	60-250	10-100

[1] Analyzed by Chulabhorn Research Institute, Thailand

[2] Analyzed by National Institute of Occupational and Environmental Health, Vietnam

[3] Water samples were analyzed before and after water treatment of arsenic contamination

Lack of Skin Lesions in Vietnam

Daily intake (μg/day) of inorganic As in different populations.

Country	Mean	Min	Max	Remarks	References
Arsenic contaminated site					
Vietnam[a]	682	67	1520		This study
Chile	1389	475	1647	Adult males	Diaz et al. (2004)
Mexico[b]	1220	320	3100	Summer	Del Razo et al. (2002)
Mexico[b]	899	198	1713	Winter	Del Razo et al. (2002)
India 1[c]	708			Adult males	Roychowdhury et al. (2003)
Bangladesh[b]	674			Adult males	Watanabe et al. (2004)
India 2[c]	564			Adult males	Roychowdhury et al. (2003)
Control site for the above site					
Chile	125	57	200	Adult males	Diaz et al. (2004)
Mexico[b]	69	18	147	Summer	Del Razo et al. (2002)
Mexico[b]	56	15	106	Winter	Del Razo et al. (2002)

[a] As in water assumed as inorganic As.
[b] Total As assumed as inorganic As.
[c] 50% of total As assumed as inorganic As.

Agusa et al, 2009; Environmental Pollution (157)

- Study investigated urinary arsenic metabolites, arsenic in rice and risk assessment for health (arsenic+rice est inorganic arsenic exp)
- Age and sex considered in methylation capacity

Health Effect?

- No evidence of skin “disorder”
- Authors cite not enough time for exposure (5-10 years)
- Wells installed 1-10 years ago
- NRC 6 months -2 years for skin lesions
- * Use of rainwater for drinking in the rainy season
- Other factors???????

Why do we see different health effects in different populations?

- Blackfoot Disease Taiwan
- Cancer?
- Diabetes
- Bronchiasis/ Lung Cancer?

Arsenic Susceptibility

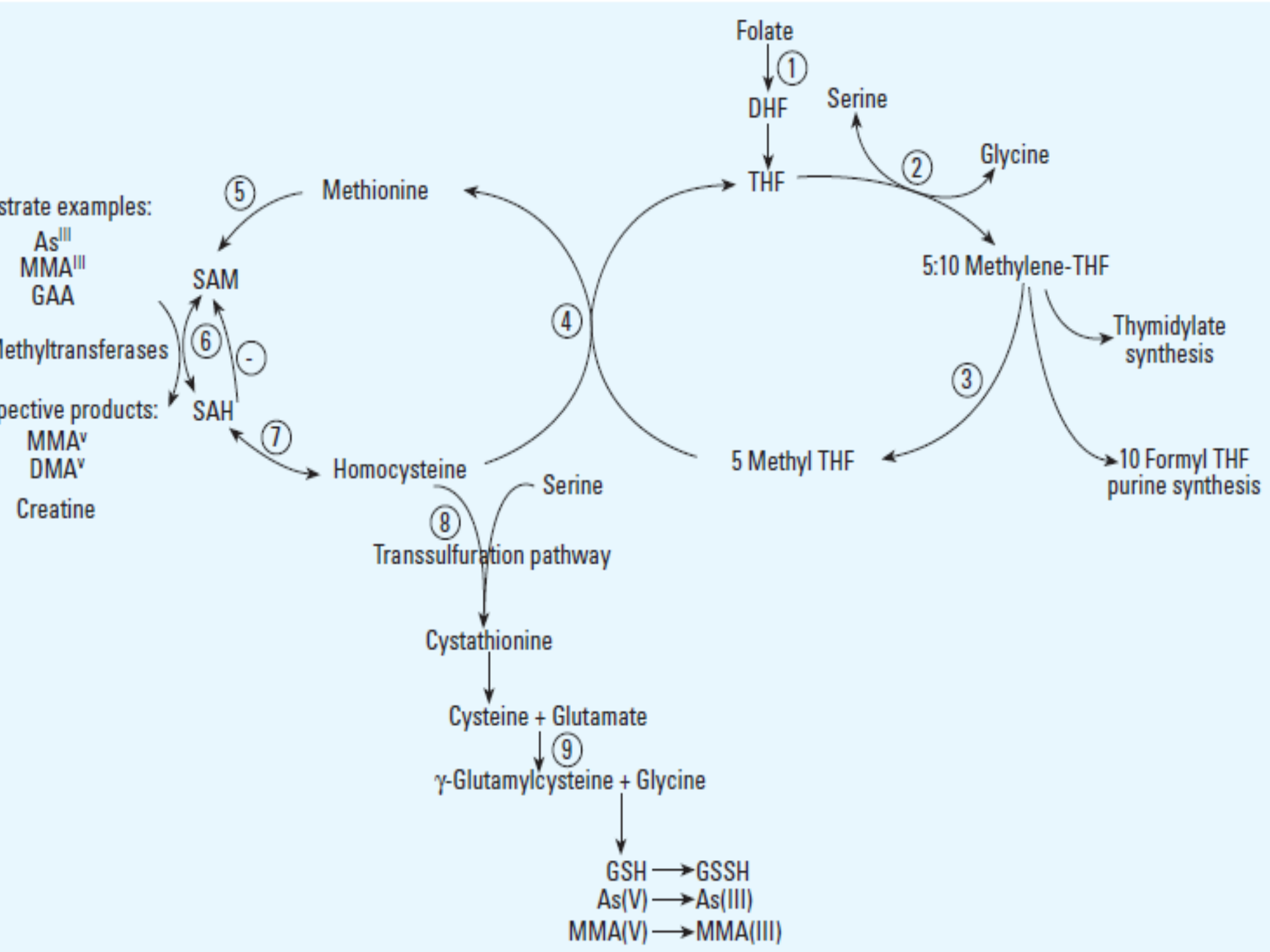
- Co-exposure to other environmental contaminants
  - UV exposure
  - Antimony
  - Manganese
  - -Smoking
  - -Betel nut
- Dose, route of exposure, duration of exposure
- Individual Factors
  - Genetics
  - Gender
  - Age
  - Nutritional status
- Methylation of inorganic arsenic

Genetic Susceptibility

- Glutathione
- Arsenic methtransferases (AS3MT)
- Metal metabolism
- DNA repair
- Oxidative stress

Diet

- Folate
- Methionine
- Protein
- Beta carotene
- Selenium


Folate
1
DHF
Serine
THF
2
Glycine
5
Methionine
strate examples:
As[III]
MMA[III]
GAA
SAM
5:10 Methylene-THF
4
Thymidylate synthesis
lethyltransferases
6
-
3
pective products:
MMA[V]
DMA[V]
Creatine
SAH
7
5 Methyl THF
10 Formyl THF purine synthesis
Homocysteine
Serine
8
Transsulfuration pathway
Cystathionine
Cysteine + Glutamate
9
γ-Glutamylcysteine + Glycine
GSH → GSSH
As(V) → As(III)
MMA(V) → MMA(III)

Nepal

- Half a million people inhabiting the region are believed to have been exposed to arsenic levels greater than 50 microg/L in their drinking water.
- Thirty-one percent of the population (3.5 million) in the region are estimated to have been exposed to arsenic levels between 10 and 50 microg/L

Nepal: Hindu Communities

- The six-eating occasion analysis revealed that gender differences in food intake of rural Nepalese adults occurred during lunch and daytime snack, attributing to gender differences in daily activity patterns

Sudo et al, 2009

- Gender differences in per-day energy and protein intakes were related to sex differences in body size and energy expenditure.
- Apparent gender differences in the crude intakes disappeared when they were expressed by nutrient density (mg or microg/MJ) since micronutrient intakes were significantly correlated with energy intake.
- Males' iron intake was larger even after adjustment for energy intake, attributing to their larger portion sizes of commonly consumed staple foods and higher frequencies of consuming luxury foods (fish and tea).
- CONCLUSION: The intrahousehold unequal distribution of food incurs risk of iron deficiency among female subjects.

Sudo et al 2006

*Similar to Bangladesh

How do the diets differ in these countries compared to Argentina and Bangladesh?

- Seasonality in terms of diet
- Nutritional differences
- Cultural difference in terms of who consumes which types of foods

Lifestyle Factors

Environmental Co-Exposures

- UV exposure
- Occupational exposures
- Antimony
- Manganese
- Unknown Factors???

Needs for further study

- Characterization of the variability in exposure in each region
- Understanding of the exposure sources (especially in areas where sand filtration is in place)
- Understanding of unique cultural, dietary, environmental exposures which influence susceptibility in these regions
- Coordinated studies with biomarkers to validate environmental monitoring
- Multi-disciplinary teams working in the same region/village/study site

Major Needs in the Global Burden of Environmental Arsenic Exposure and Human Disease

Better coordinated local and global data collection on environmental exposures in vulnerable populations related to health impacts and to disease etiologies.

- **A *global,* strategic, epidemiological effort to fill gaps in our understanding of the relationship between environmental exposure and ill health in vulnerable populations (susceptible subgroups: prenatal exposure, children)**
- **Consider the entire environmental pathway from driving forces to health impact when designing interventions to improve the environment and health of children.**
- **Understand the mechanism(s) and interactions between infectious diseases, diet, culture, environmental exposures, and genetics and predisposition in order to develop better prevention methods.**
- **Create multidisciplinary teams to address issues of hydrogeology, medicine, epidemiology, toxicology and genomics**
- **Remediation but goal is prevention**