

Global environmental epidemiology research in action: recent arsenic findings

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PERIODIC TABLE

Atomic Properties of the Elements

NIST

National Institute of Standards and Technology
Technology Administration, U.S. Department of Commerce

Frequently used fundamental physical constants
For the most accurate values of these and other constants, visit physics.nist.gov/constants
1 second = 9 192 631 770 periods of radiation corresponding to the transition between the two hyperfine levels of the ground state of ^{133}Cs

speed of light in vacuum	c	299 792 458 m s ⁻¹	(exact)
Planck constant	h	6 626 069 57 × 10 ⁻³⁴ J s	($h = h/2\pi$)
elementary charge	e	1.602 176 634 × 10 ⁻¹⁹ C	
electron mass	m_e	9.109 383 56 × 10 ⁻³¹ kg	
proton mass	m_p	1.672 621 63 × 10 ⁻²⁷ kg	
fine-structure constant	α	1/137.035 999 074	
Rydberg constant	R_∞	10 973 731.568 160 × 10 ¹⁰ m ⁻¹	
Boltzmann constant	k	1.380 650 4 × 10 ⁻²³ J K ⁻¹	

■ Solids
■ Liquids
■ Gases
■ Artificially Prepared

Physics Laboratory physics.nist.gov		Standard Reference Data Group www.nist.gov/srd				2
13 IIIA	14 IVA	15 VA	16 VIA	17 VIIA	18 VIIIA	He
5 B Boron 10.811 [10.811] 5.2965	6 C Carbon 12.0107 [12.0107] 11.2603	7 N Nitrogen 14.0064 [14.0064] 11.5341	8 O Oxygen 15.9994 [15.9994] 11.1911	9 F Fluorine 18.9984032 [18.9984032] 7.3125	10 Ne Neon 20.1797 [20.1797] 2.5061	
13 Al Aluminum 26.981538 [26.981538] 5.6856	14 Si Silicon 28.0855 [28.0855] 8.4512	15 P Phosphorus 30.973761 [30.973761] 10.4857	16 S Sulfur 32.059 [32.059] 10.3630	17 Cl Chlorine 35.453 [35.453] 12.9675	18 Ar Argon 39.948 [39.948] 15.7501	
31 Ga Gallium 69.723 [69.723] 5.6831	32 Ge Germanium 72.64 [72.64] 7.6034	33 As Arsenic 74.9216 [74.9216] 8.7855	34 Se Selenium 78.96 [78.96] 7.7524	35 Br Bromine 79.904 [79.904] 8.1458	36 Kr Krypton 83.904 [83.904] 11.0009	
49 In Indium 114.818 [114.818] 5.7864	50 Sn Tin 118.710 [118.710] 7.3439	51 Sb Antimony 121.760 [121.760] 8.6286	52 Te Tellurium 127.60 [127.60] 8.0000	53 I Iodine 126.90447 [126.90447] 8.4171	54 Xe Xenon 131.29 [131.29] 12.7339	
81 Tl Thallium 204.38 [204.38] 8.9802	82 Pb Lead 207.2 [207.2] 8.4107	83 Bi Bismuth 208.98039 [208.98039] 7.2855	84 Po Polonium 209 [209] 8.114	85 At Astatine 209 [209] 8.114	86 Rn Radon 222 [222] 16.7991	
	114 Uuq Ununquadium (289)		116 Uuh Ununhexium (292)			
66 Dy Dysprosium 162.501 [162.501] 5.9102	67 Ho Holmium 164.93032 [164.93032] 6.0211	68 Er Erbium 167.259 [167.259] 6.1017	69 Tm Thulium 168.93481 [168.93481] 6.1943	70 Yb Ytterbium 173.04 [173.04] 6.2542	71 Lu Lutetium 174.967 [174.967] 6.2525	
98 Cf Californium 251 [251] 9.2917	99 Es Einsteinium 252 [252] 9.42	100 Fm Fermium 257 [257] 9.50	101 Md Mendelevium 258 [258] 9.58	102 No Nobelium 259 [259] 9.55	103 Lr Lawrencium 262 [262] 9.77	

Symbol	Atomic Number	Ground-state Level
Ce	58	G ³
Cerium		
140.116		
[Xe]4f5d6s ²		
5.5387		
Ground-state Configuration		
Ionization Energy (eV)		

Based upon ^{12}C . {} indicates the mass number of the most stable isotope

For a description of the data, visit physics.nist.gov/data

NIST SP 956 (September 2003)

The Berkeley Arsenic Health Effects Research Group (ASRG)

Arsenic Research Group

Not

Allan Smith's Research Group

Associate Director: Craig Steinmaus



The Berkeley Arsenic Health Effects Research Program

Our focus is on highly exposed populations, with a range of exposure usually including some with more than 500 ug/L in water, in order to have good statistical power to detect real effects, with scientific plausibility.

Populations in which we conduct studies include:

- **USA: California and Nevada**
- **Argentina (Cordoba)**
- **Chile (Northern)**
- **India (West Bengal)**
- **Bangladesh (Matlab)**

What does arsenic in water cause?

When I was asked by the State of California in 1989 to assess the risks from arsenic in drinking water the only established outcomes were skin lesions and skin cancer.





Source: Project Well, West
Bengal, India, 2003

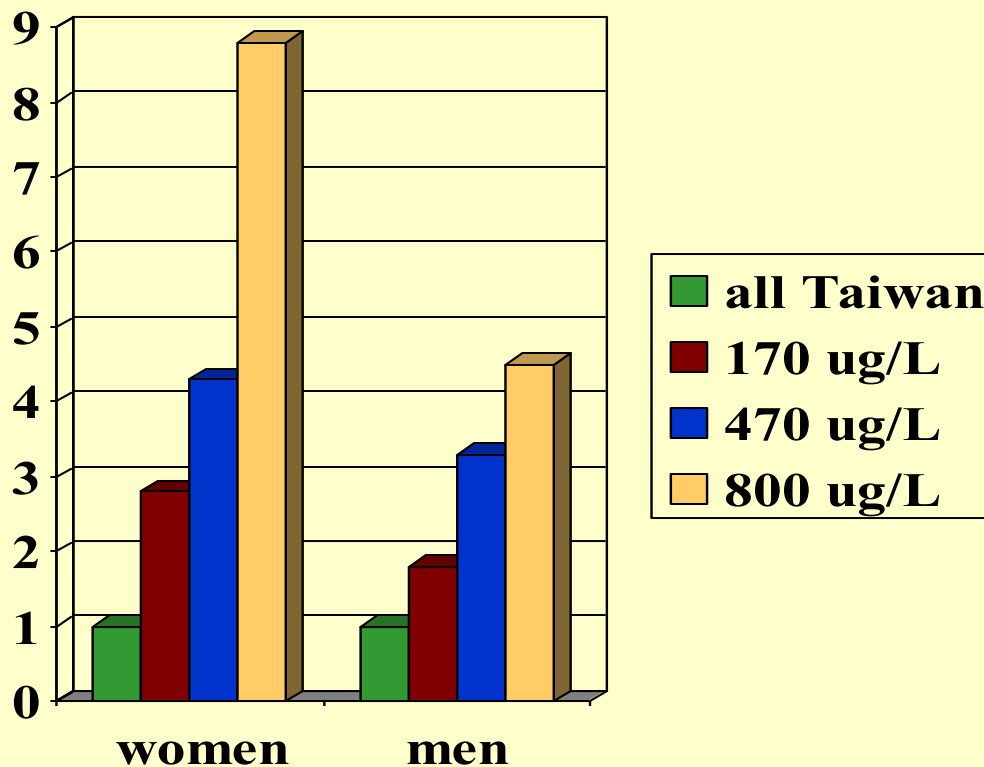






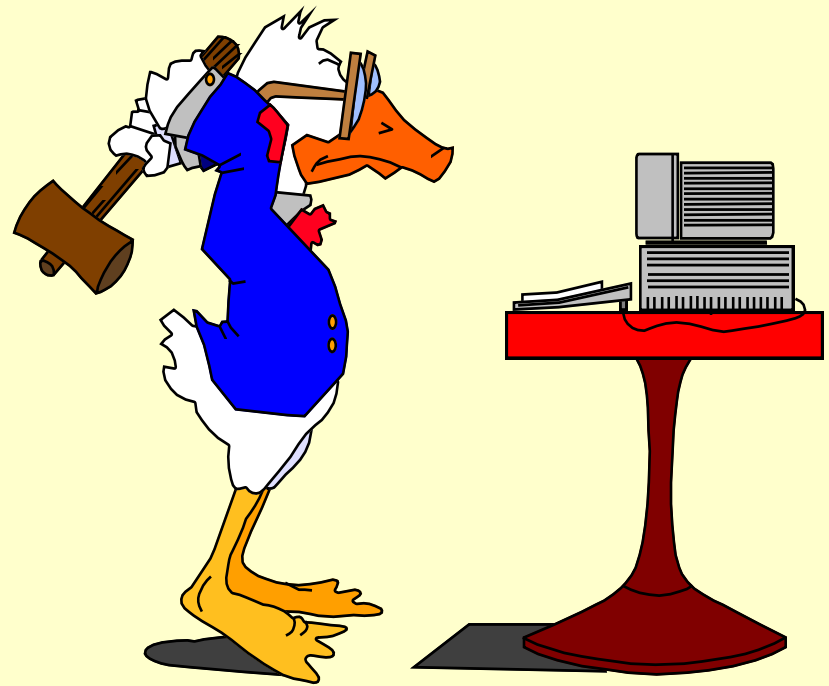
Lung cancer and arsenic in Taiwan

adapted from CJ Chen et al 1988



- Comparison population, all of Taiwan
- vertical axis: age adjusted rate ratios (relative risk)

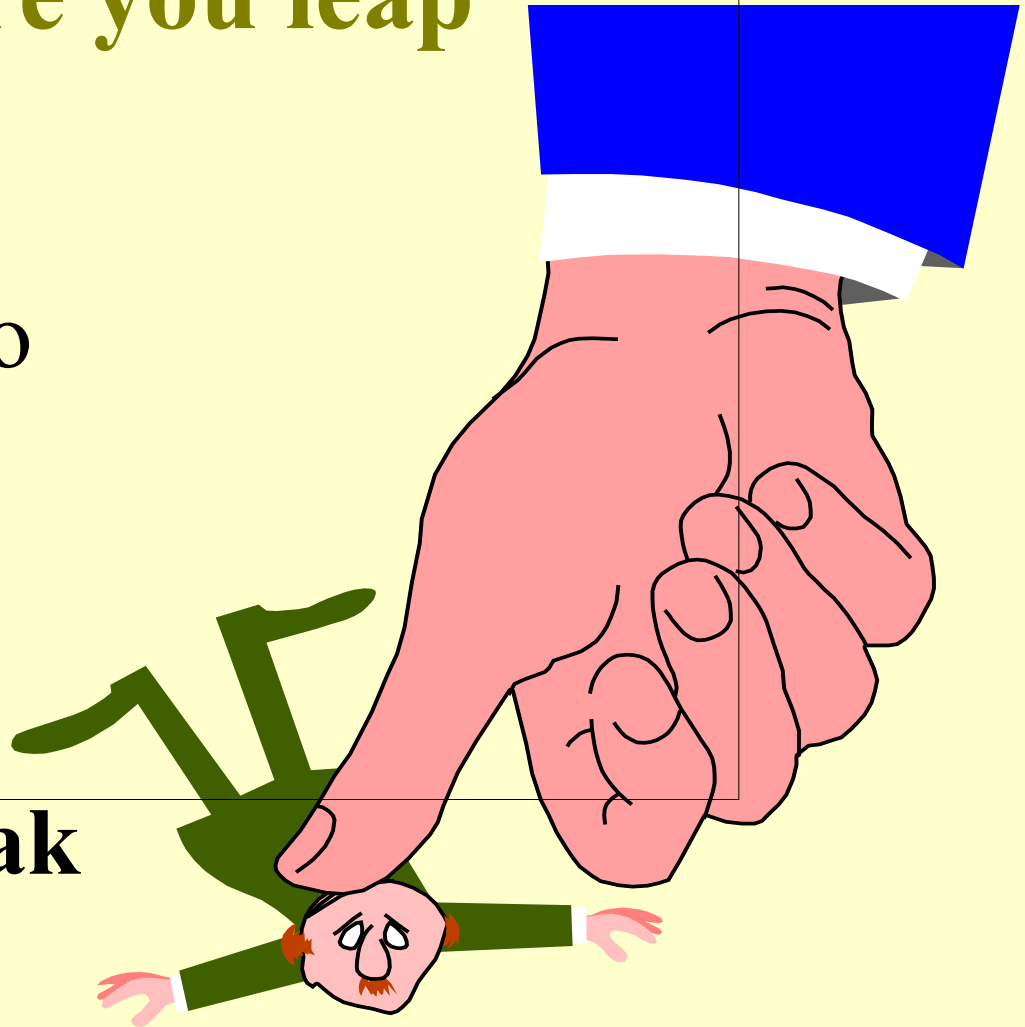
Bias You got the wrong answer



So, look before you leap

And in
epidemiology, to
stay alive,

**consider bias
before you squeak**



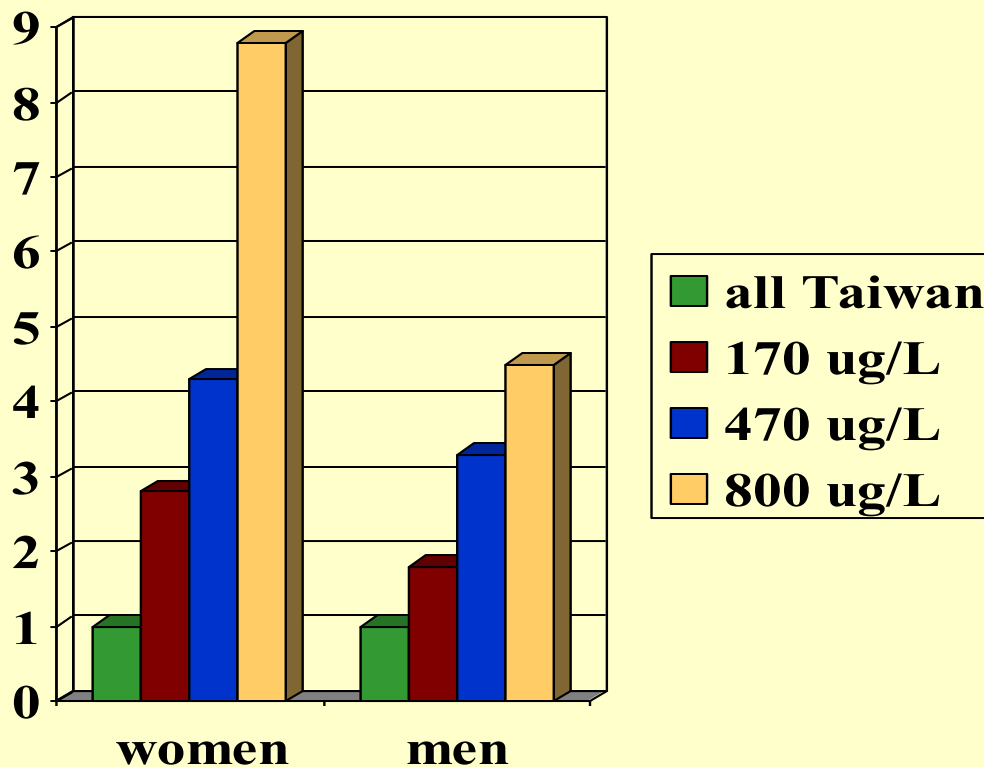
**It is surprising that arsenic in
drinking water would have major
effects in the lungs**

Known causes of lung cancer involve inhalation

- smoking
- passive smoking
- asbestos
- radon
- silica
- chromium
- diesel exhaust
- coke oven PAHs
- bischlormethyl ether
- nickel
- arsenic

Lung cancer and arsenic in Taiwan

adapted from CJ Chen et al 1988



- Comparison population, all of Taiwan
- vertical axis: age adjusted rate ratios (relative risk)

Bladder cancer mortality associated with arsenic in drinking water in Argentina

Claudia Hopenhayn, Mary Lou Biggs, Analia Fuchs,
Remo Bergoglio, Enrique E. Tello, Hugo Nicolli,
Smith AH

Epidemiology 1996; 7: 117-124

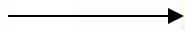
Unos de los Primeros Estudios y Publicaciones del Arsénico en el Agua en Córdoba

- **Ayerza A. Arsenicismo regional endémico. Bol Acad Nac Med, 1917. “Enfermedad de Bell Ville”.**
- **Bergoglio RM. Mortalidad por cáncer en zonas de aguas arsenicales de la Provincia de Córdoba, República Argentina. Pensa Médica Argentina, 1964. Cáncer urinario, y otros. Primer en el mundo.**
- **Tello EE. Estado actual del problema de los epiteloma hidroarsenicales. Rev Fac Cien Med Univ Nac Córdoba, 1972.**
- **Biagini RE. Hidroarsenicismo crónico en la República Argentina. Med Cután Ibero Latinoam, 1975.**



CHILE

Region II



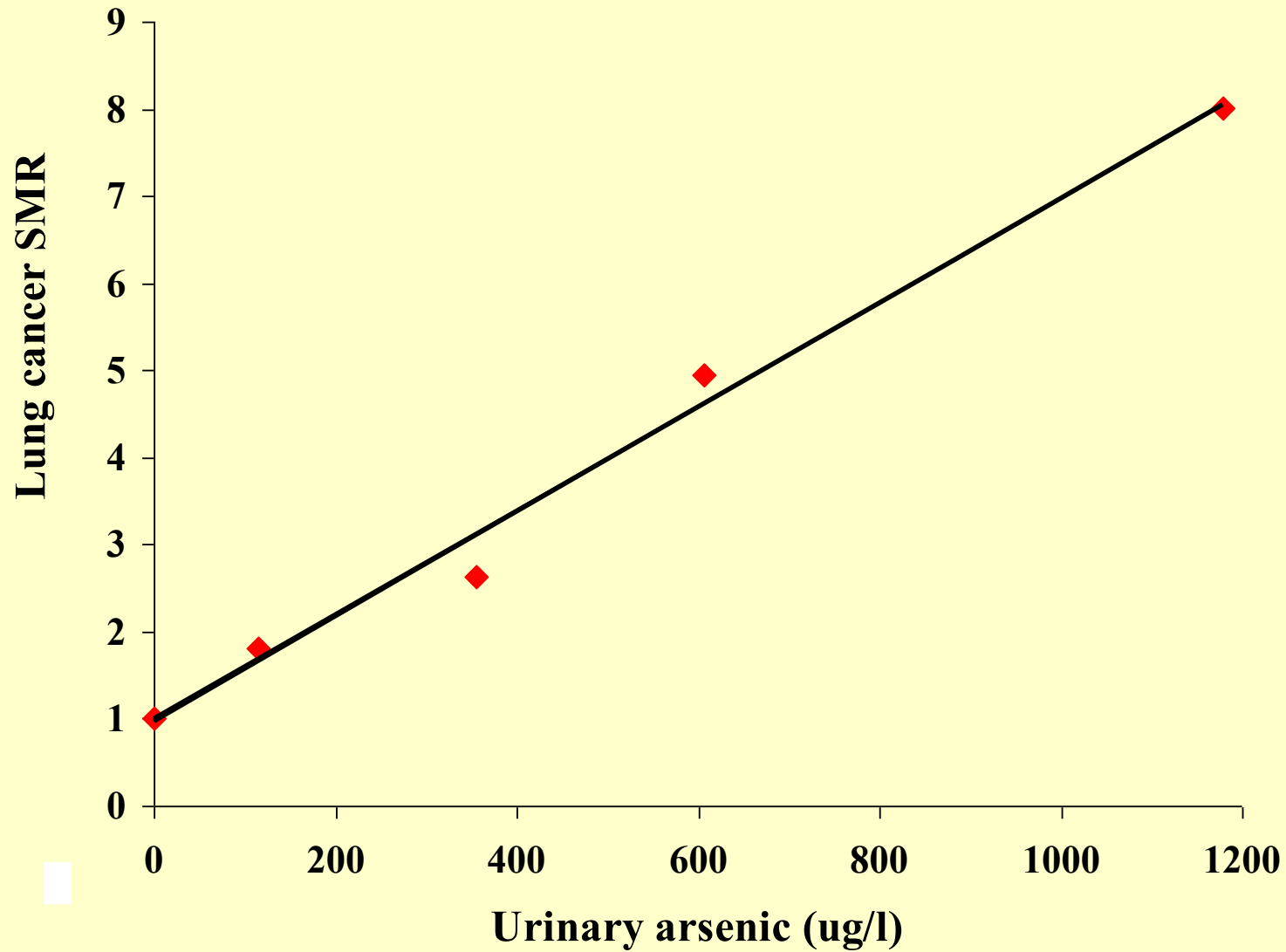
Region V



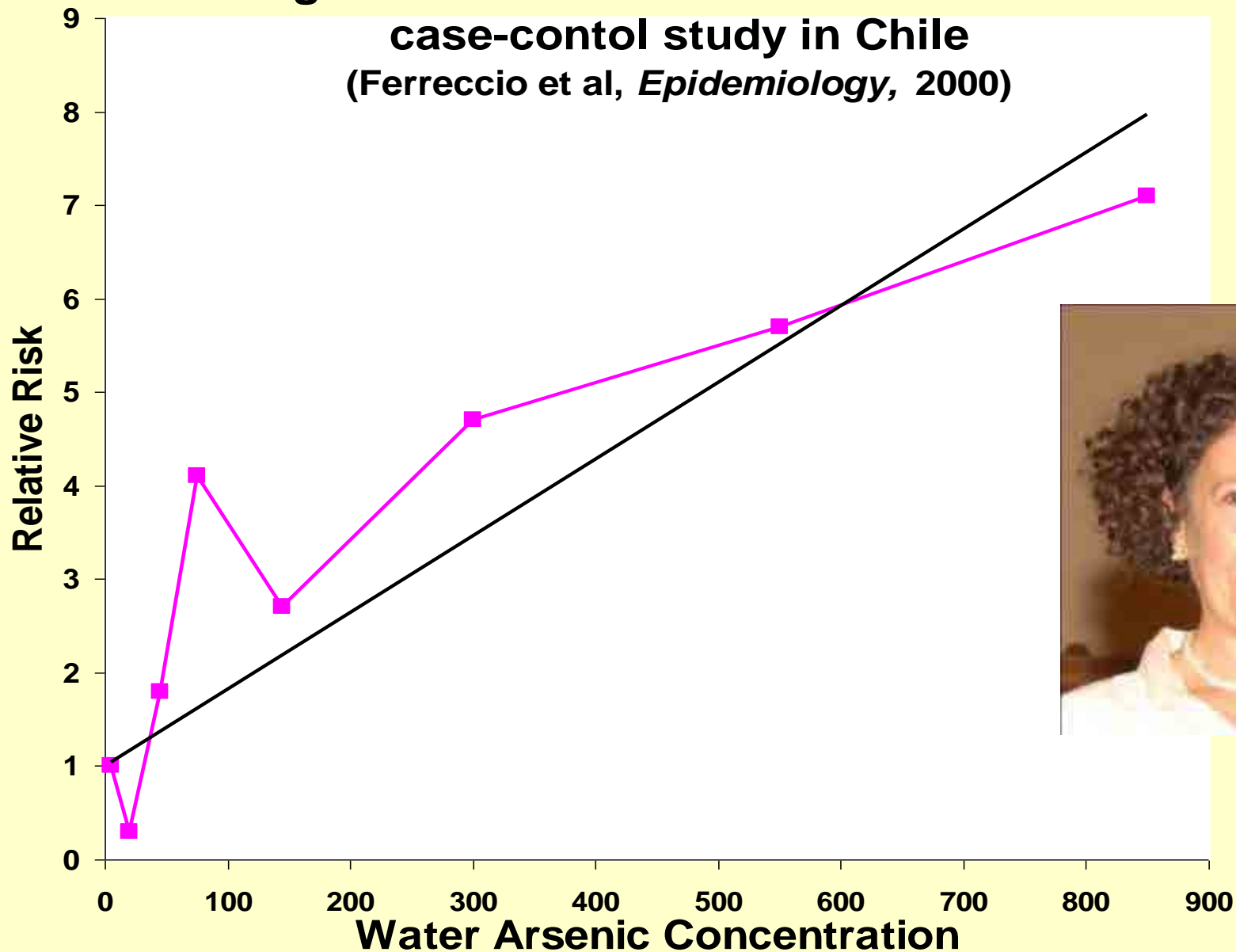
Lung Cancer Mortality Region II Chile, 1989-1993

Age Group	30-39	40-49	50-59	60-69	70-79	SMR	p value
Women							
Observed	5	23	21	41	47		
Expected	1.2	3.0	8.0	16.0	13.3		
O/E	4.2	7.7	2.6	2.6	3.5	3.1	p<0.001
Men							
Observed	14	48	142	177	129		
Expected	1.2	8.1	28.5	61.8	32.1		
O/E	11.7	5.9	4.9	2.9	4.0	3.8	p<0.001

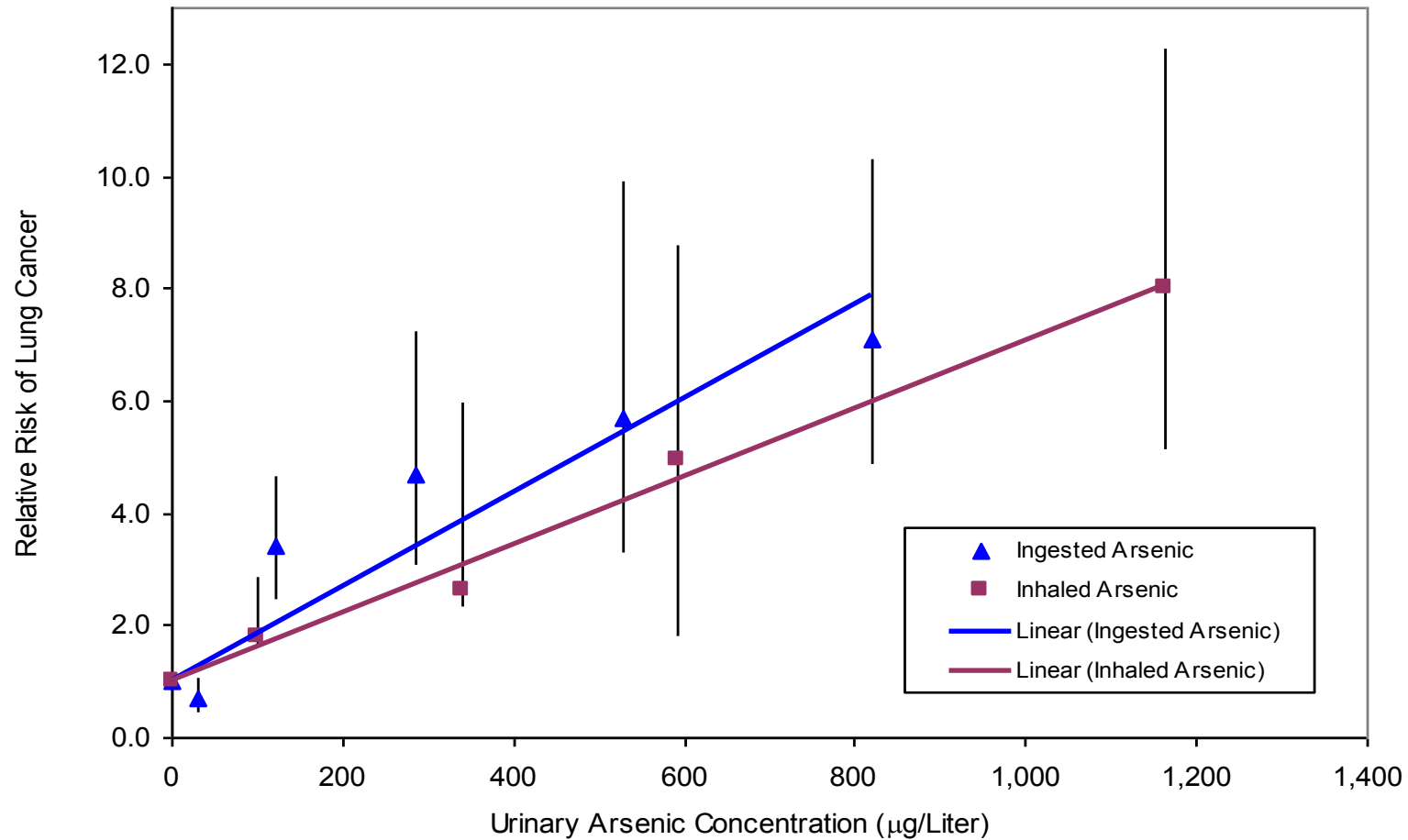
Lung Cancer and Inhalation of Arsenic



Lung cancer relative risk estimates from a case-control study in Chile (Ferreccio et al, *Epidemiology*, 2000)



Increased lung cancer risks are similar whether arsenic is ingested or inhaled.



IARC classification, 2002

Arsenic in drinking-water was evaluated as *carcinogenic to humans* (Group 1) on the basis of *sufficient evidence* for an increased risk for cancer of the urinary bladder, **lung** and skin.

Cancer risks from arsenic in drinking water

At the current standard of **50 ug/L**, the lifetime risk of dying from cancer from drinking 1 L/day of water could be as high as **13 per 1000** persons

Environmental Health Perspectives 97:259-267, 1992



Martyn Smith

The estimated cancer risk at the drinking water standard of 50 µg/L for arsenic is more than 100 times greater than that for any other drinking water contaminant

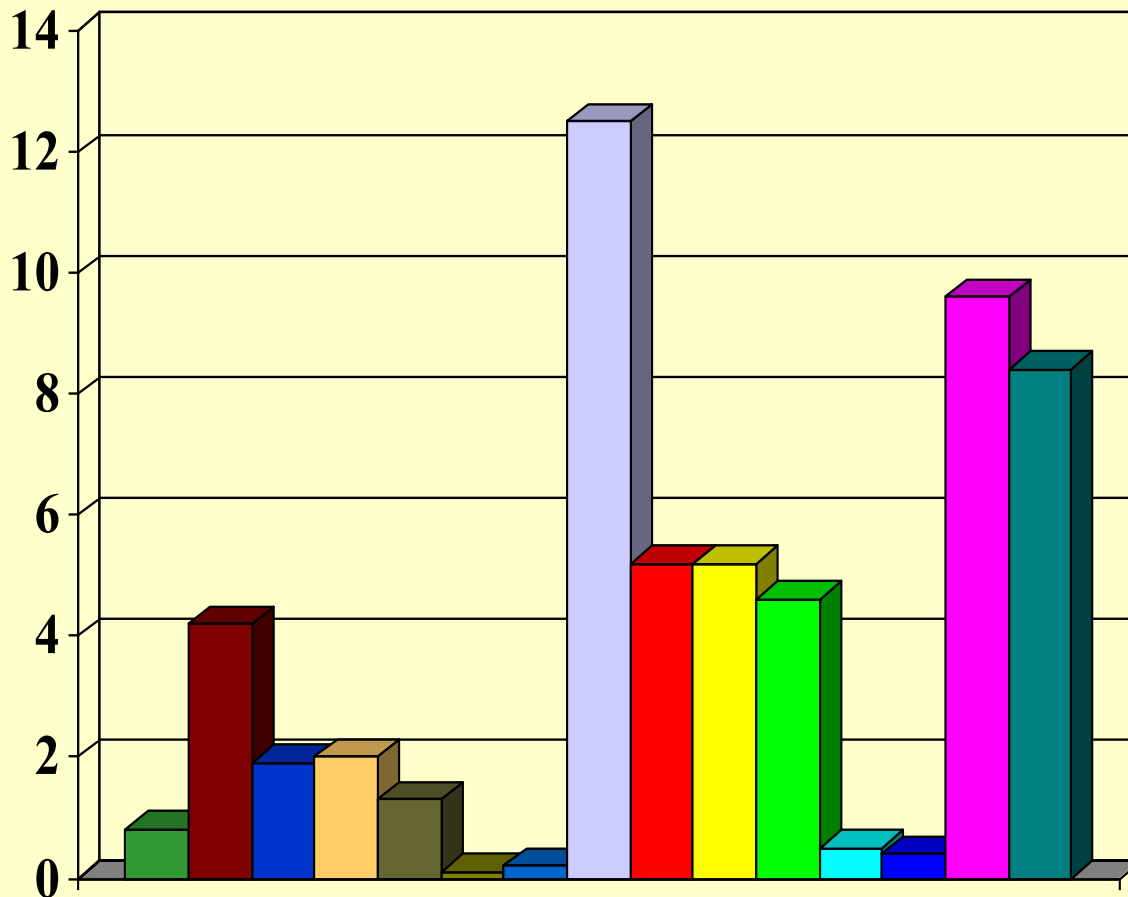
Smith AH, Lopipero PA, Bates MN, Steinmaus CM.

Arsenic epidemiology and drinking water standards.

Science 296: 2145-6, 2002

Cancer risk from contaminants in drinking water other than arsenic

Per 100,000

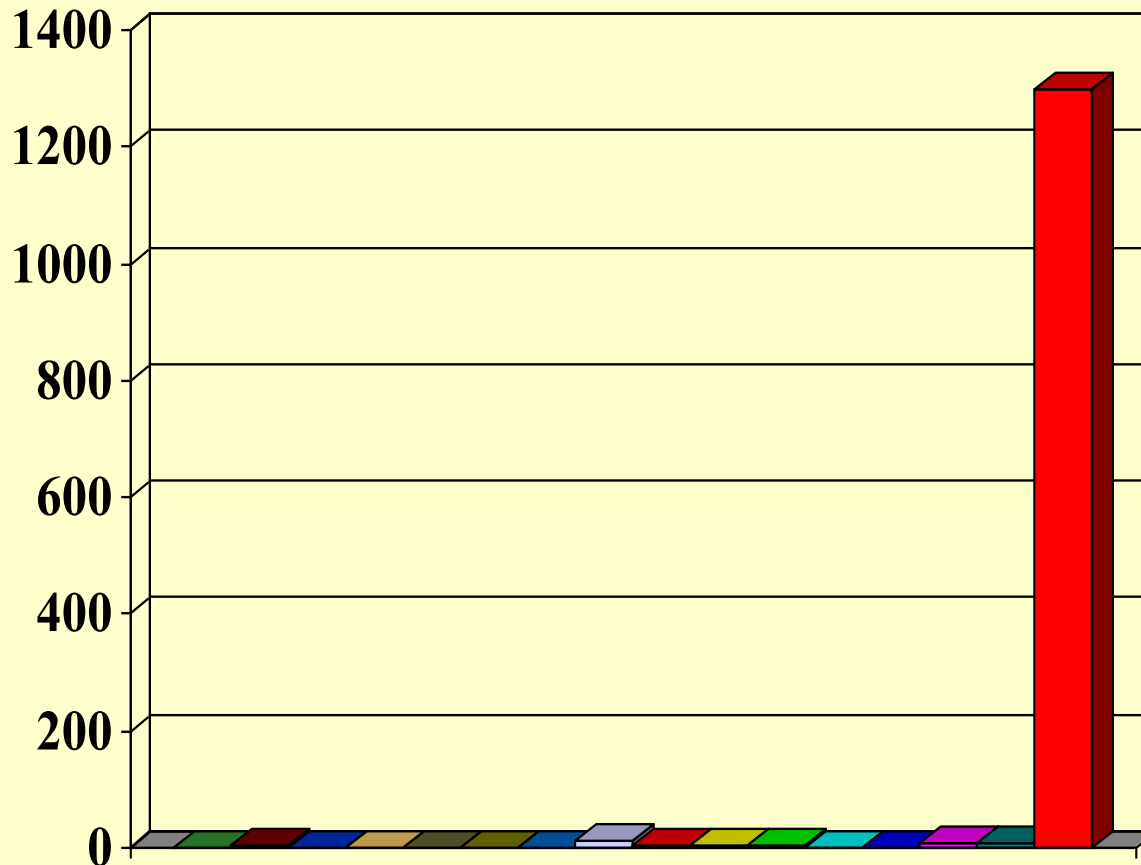


Top of the list:

Ethylene dibromide

Cancer risk from contaminants in drinking water including arsenic

Per 100,000



Cancer risks from arsenic at the old drinking water standard were >100 times higher than the next highest risk contaminant

Cancer risks from arsenic in drinking water

Lung cancer and smoking

- 10 ug/L 1 in 500 die
- 50 ug/L 1 in 100 die married to a smoker
- 500 ug/L 1 in 10 die active smoker
- 5000 ug/L all die

**And arsenic in water looks good, does not smell
and has no taste. So the risks are unbelievable**

**Arsenic in drinking water results in the
highest known toxic substance disease
risks and mortality from any
environmental exposure**

End Stage Lung Disease

Obstruction, Infection, Hemoptysis, Bronchiectasis

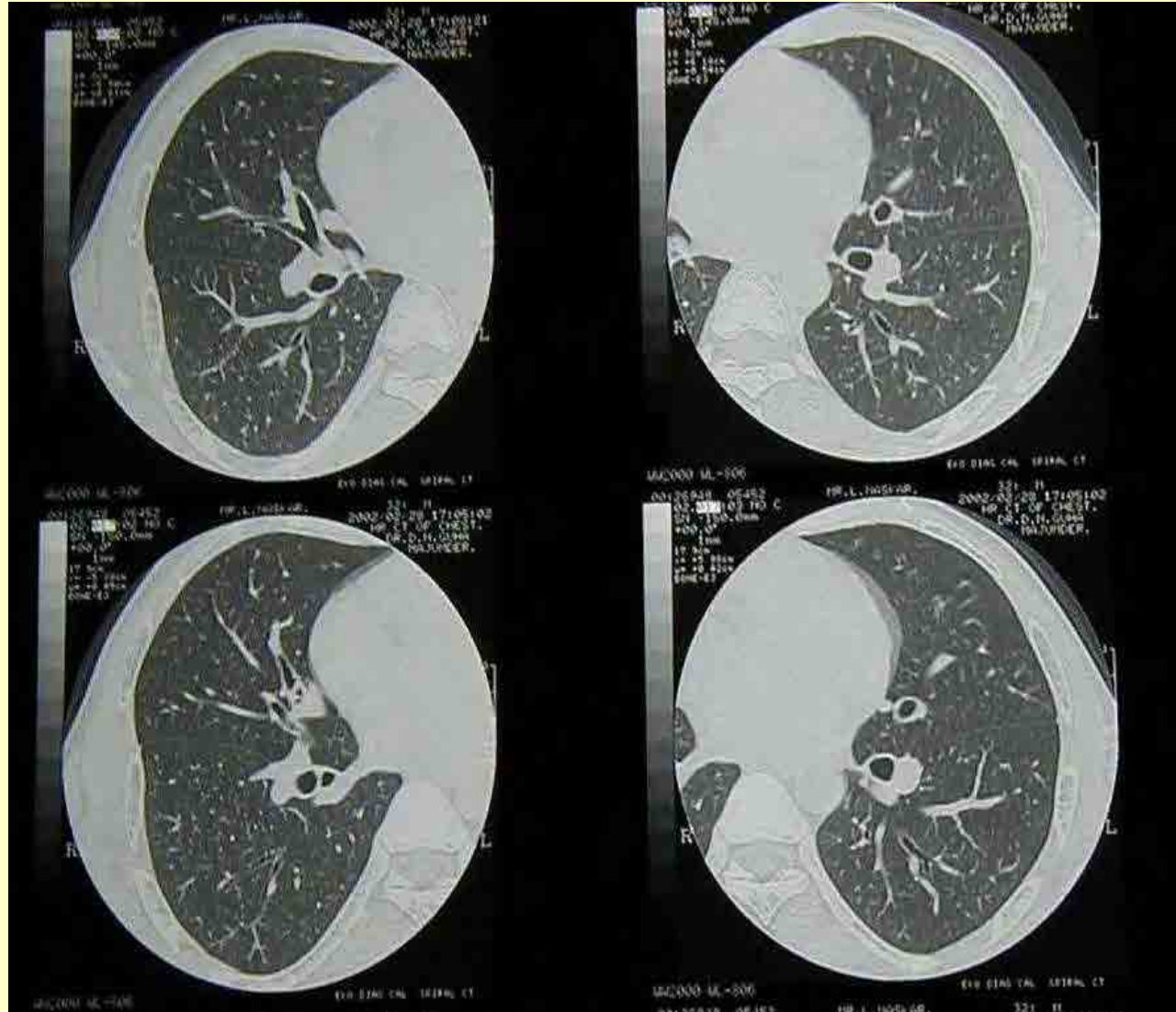


Non-malignant pulmonary effects

We believe that the first evidence of arsenic in drinking water causing non-malignant pulmonary effects came from Antofagasta in Chile, when river water with a high concentration (about 850 $\mu\text{g/L}$) of naturally occurring arsenic was first diverted to the city for use as municipal water supply in 1958.

Beginning in 1962, patients (including children) with arsenic-caused skin lesions and bronchopulmonary effects, including chronic cough and **bronchiectasis**, were identified. (Borgono et al, 1977)

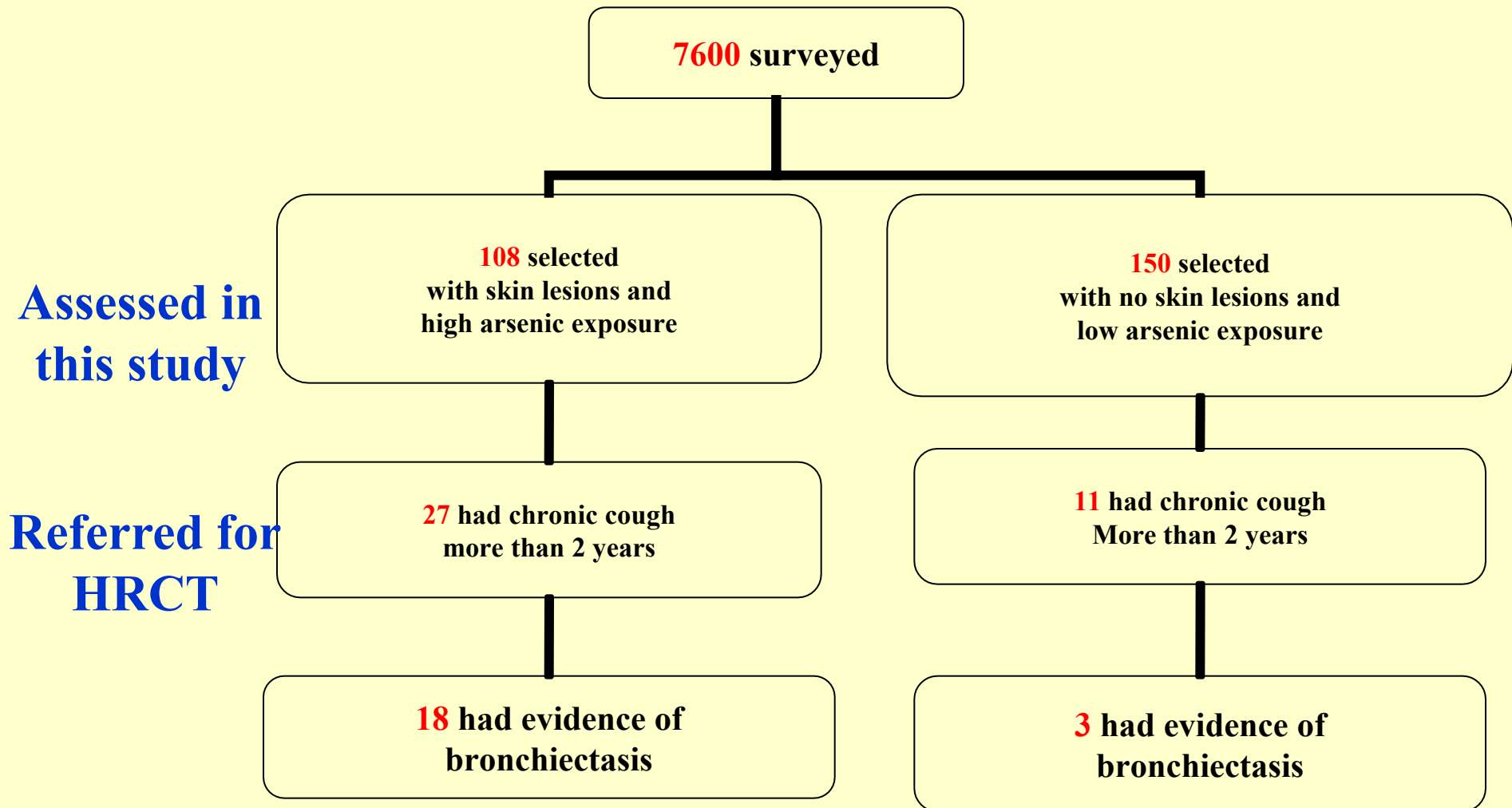
High resolution computed tomography (HRCT) with readings in India and the United States without knowing who had arsenic skin lesions.



Dr. D. N. Guha Mazumder

Craig Steinmaus

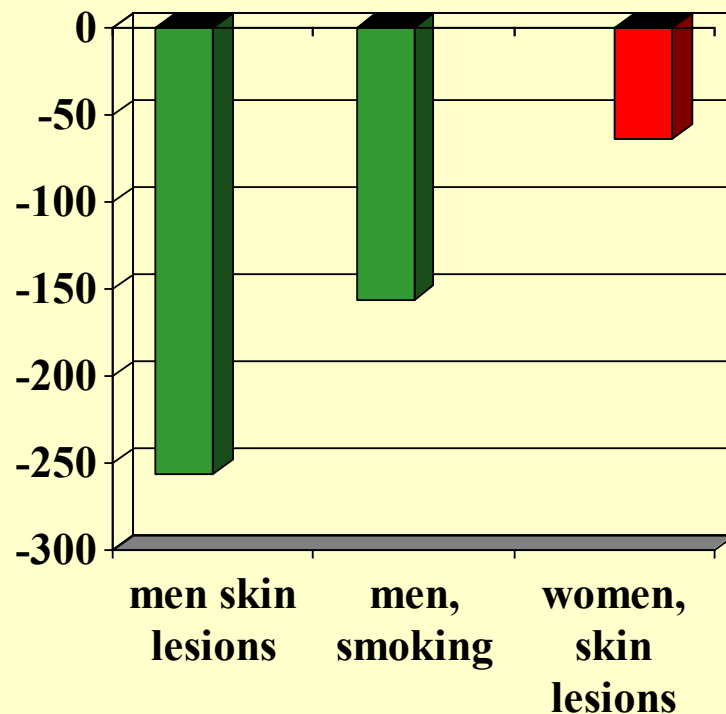
Study design, x-ray (HRCT) study in West Bengal, India



10-fold increased prevalence of bronchiectasis OR=10.1, $p<0.01$

Epidemiology 2005

Lung function findings of reduced FEV1 adjusted for age and height



- For all men combined **P=0.007**
- Among men in this population, arsenic- caused skin lesions were associated with a greater FEV1 reduction (-256ml) than from smoking (-156ml)

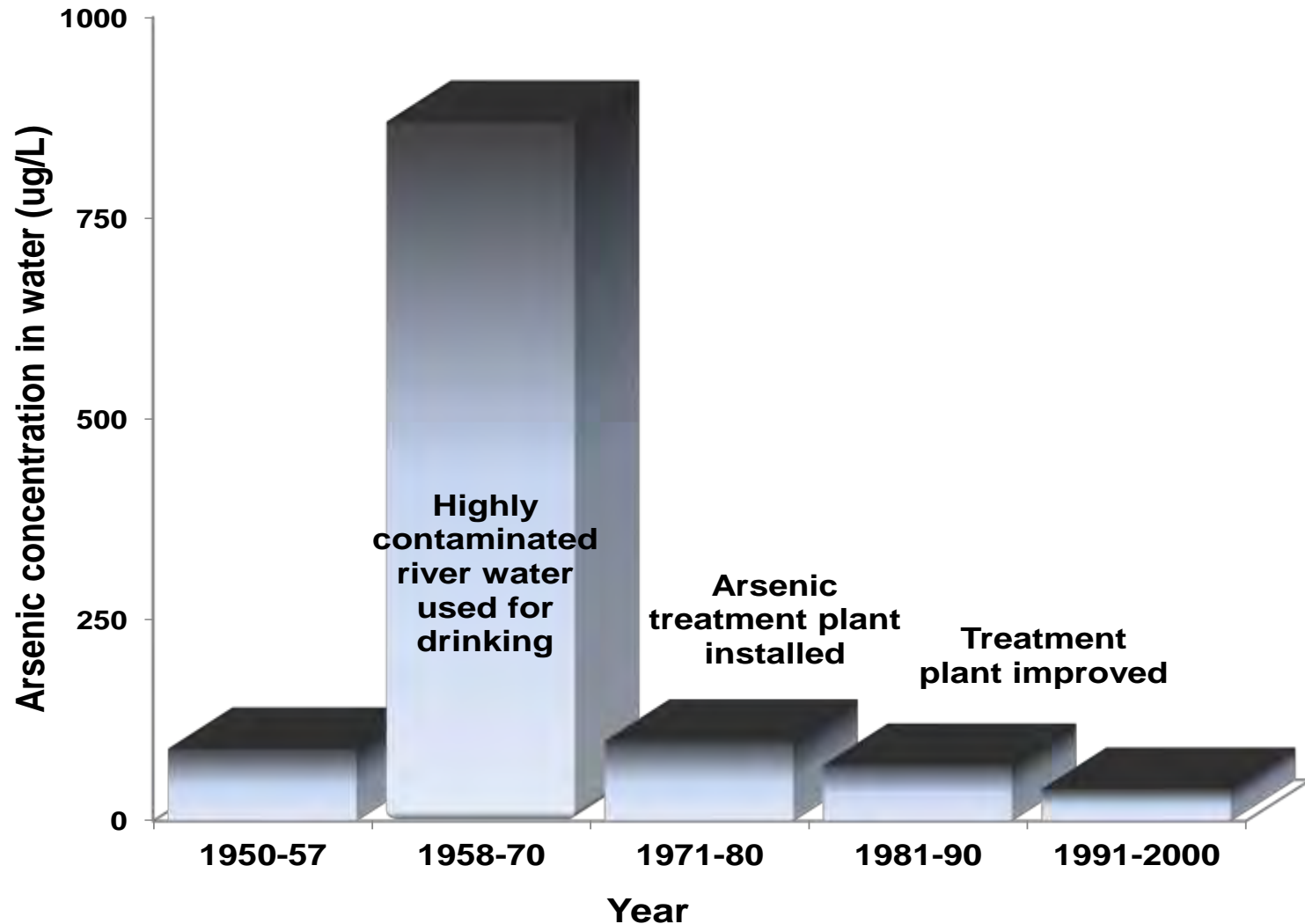
Cardiovascular disease

The first evidence of a link between cardiovascular disease and arsenic in drinking water came in **1980** from Antofagasta, Chile, with a report of **17 deaths from myocardial infarction in people under the age of 40**. (Zaldivar, 1980).

Later, a comprehensive body of evidence from a series of studies in Taiwan starting in 1988 found that arsenic in water was associated with increased mortality from cardiovascular disease.

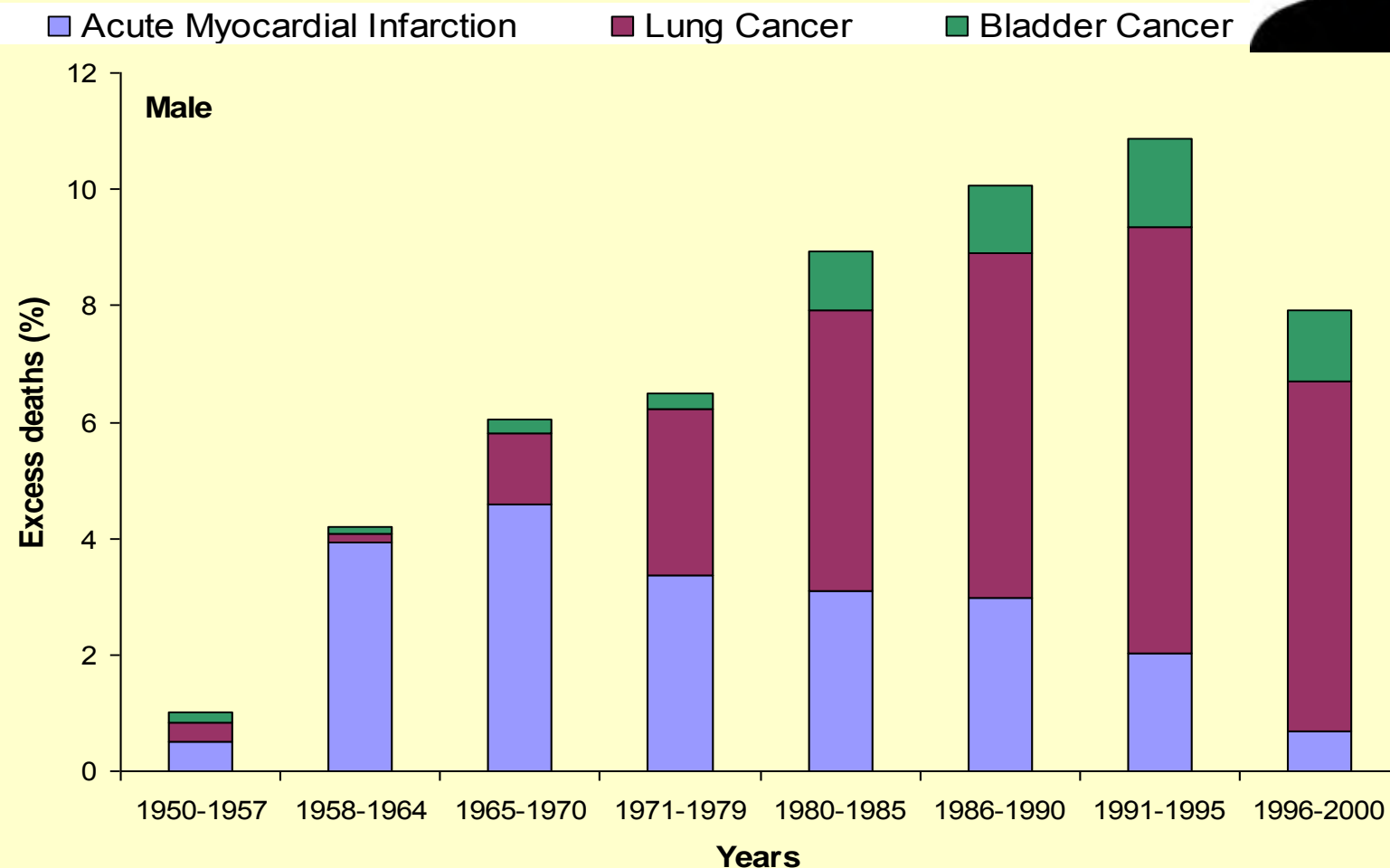
In 2007, cardiac effects including QT prolongation were shown to be associated with arsenic in drinking water in China.

Arsenic water concentrations for the city of Antofagasta (population 125,000 in 1970)



Excess deaths among men in Region II of Chile from acute MI, lung cancer and bladder cancer.

Yuan Y et al. Am J Epidemiol 166:1381-1391, 2007



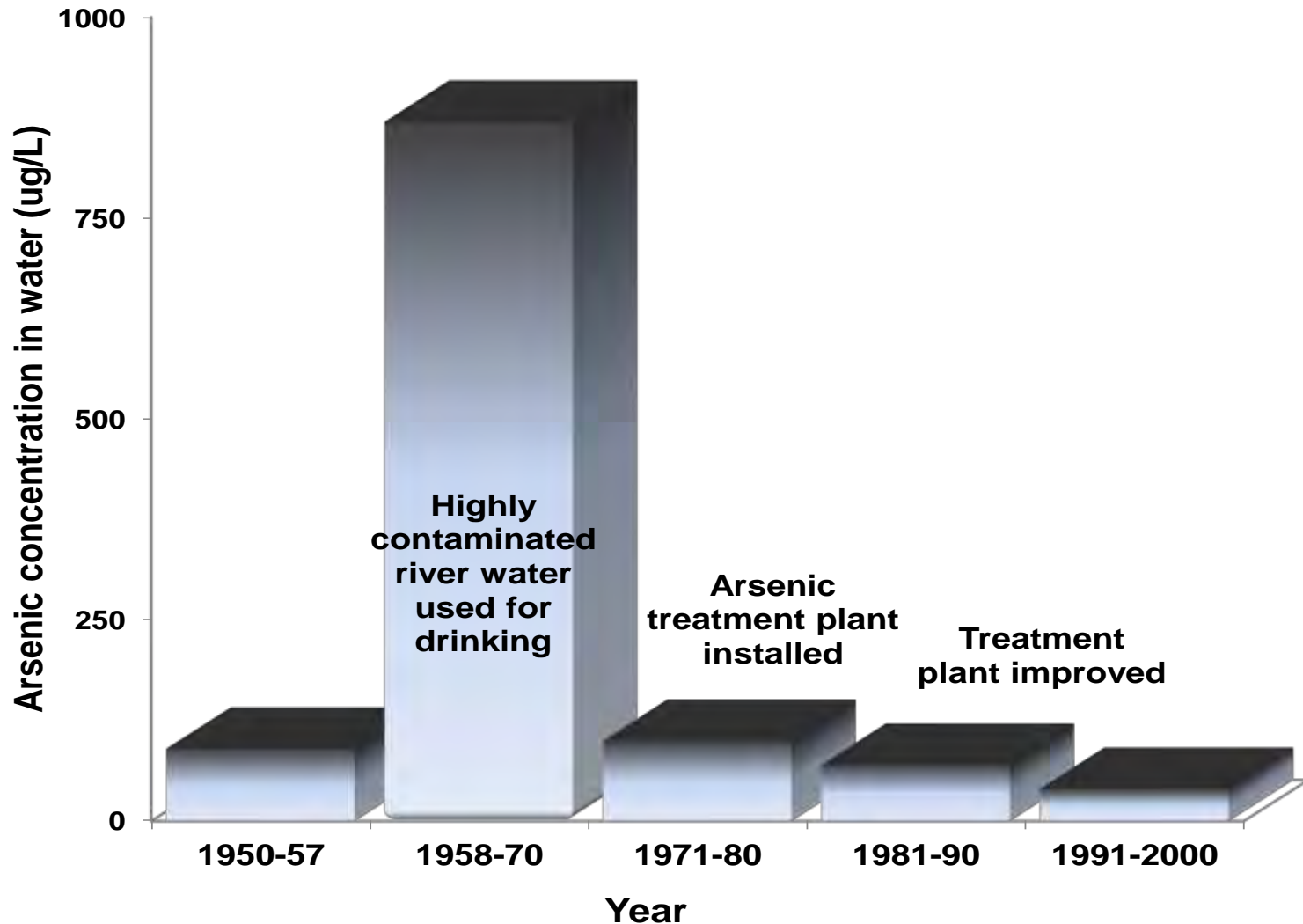
At the peak more than 1 in 10 of *all* deaths were due to arsenic

Effect of early life exposure

In utero

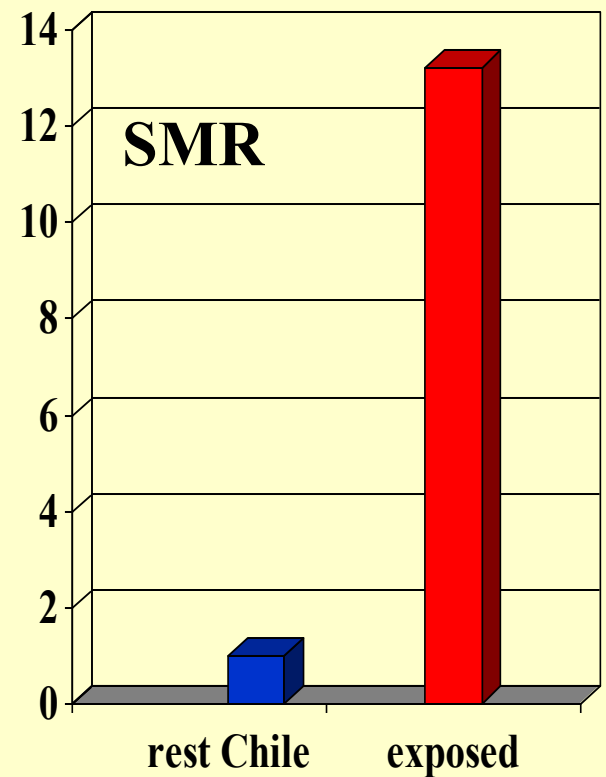
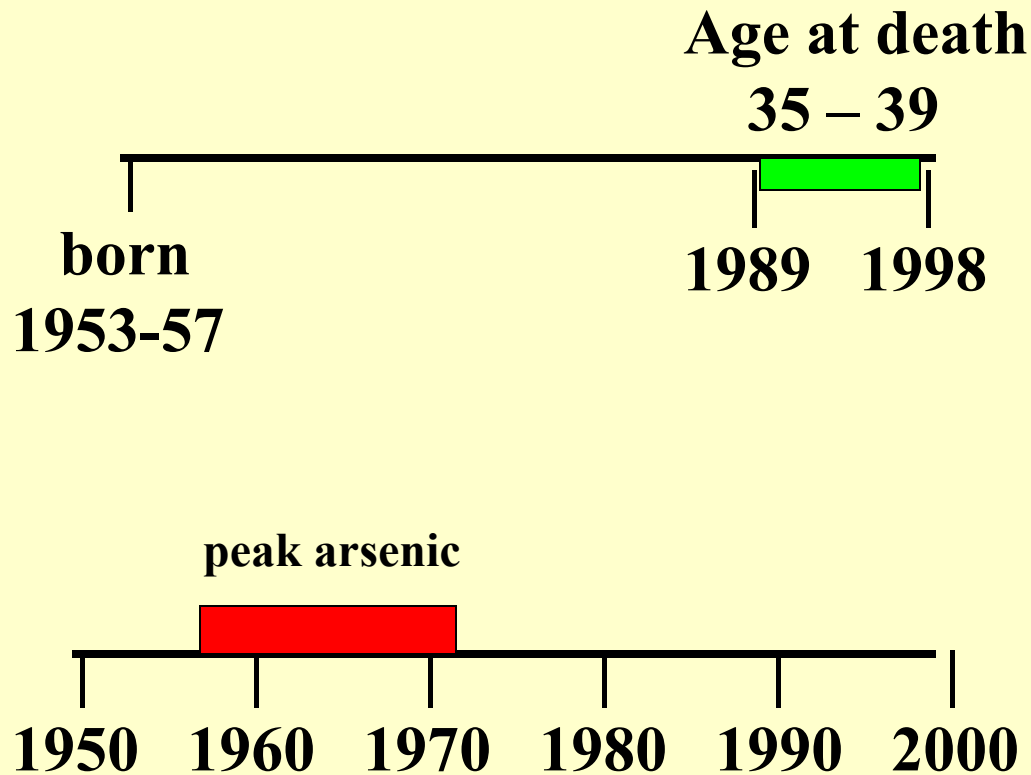
and in the first few years of childhood

Arsenic water concentrations for the city of Antofagasta (population 125,000 in 1970)



Lung cancer mortality in men according to exposure in childhood

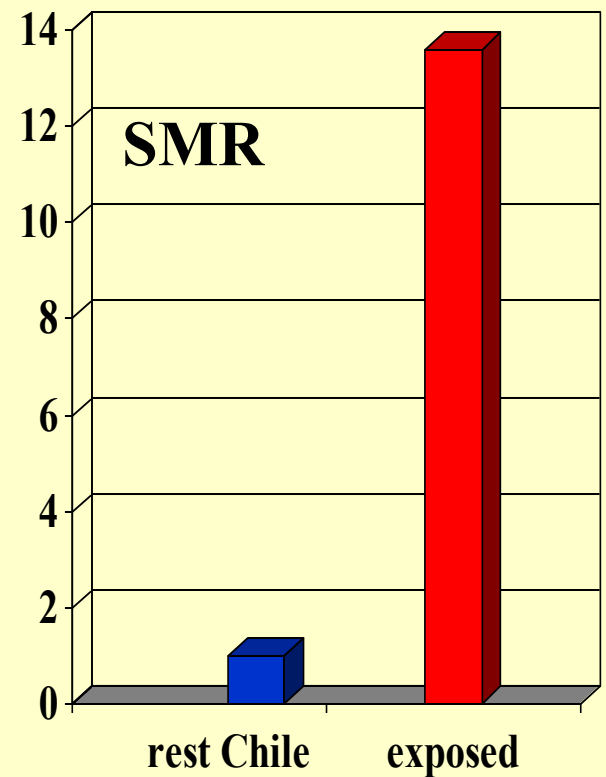
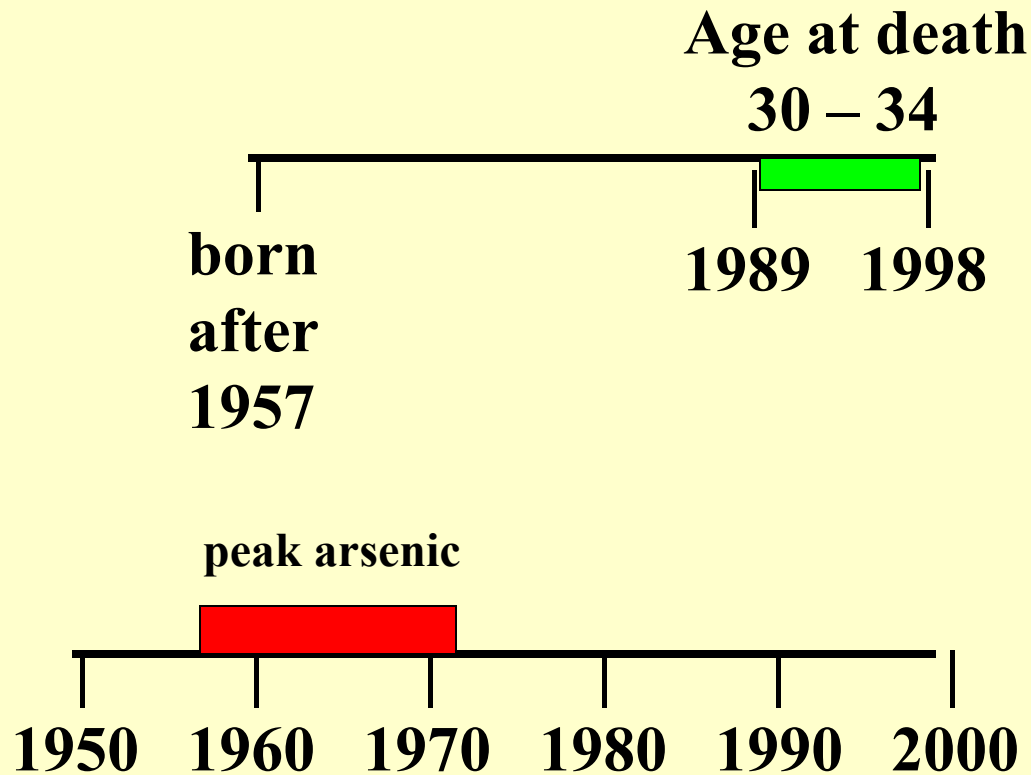
(SMR = standardized mortality ratio = observed/expected deaths)



$p < 0.001$

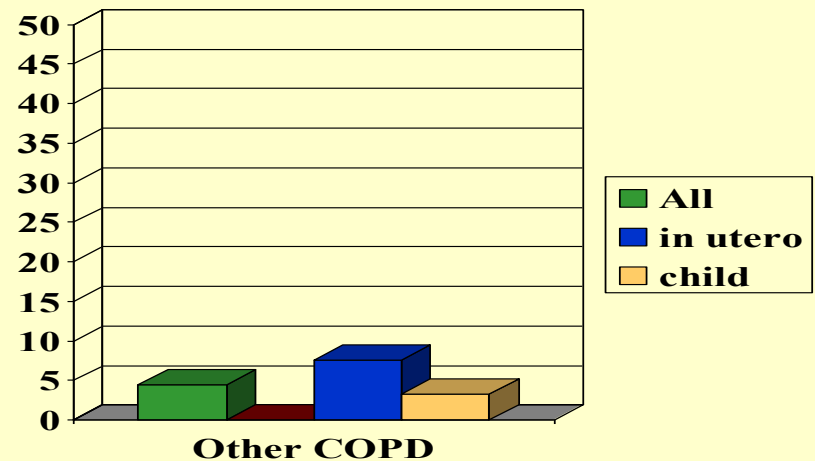
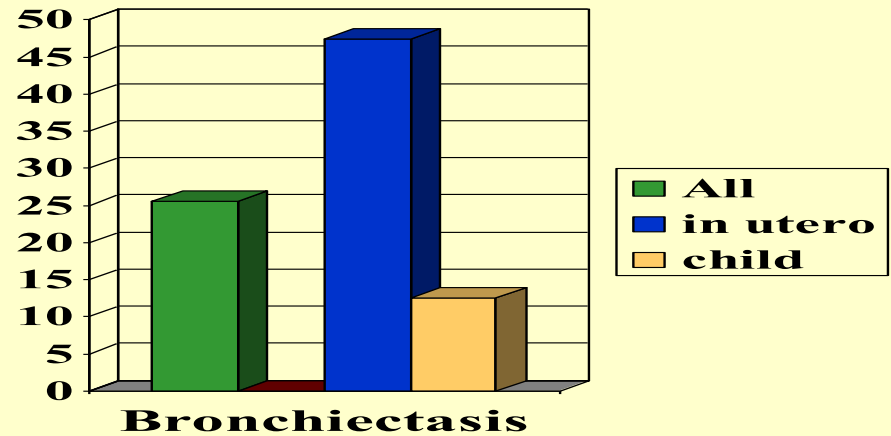
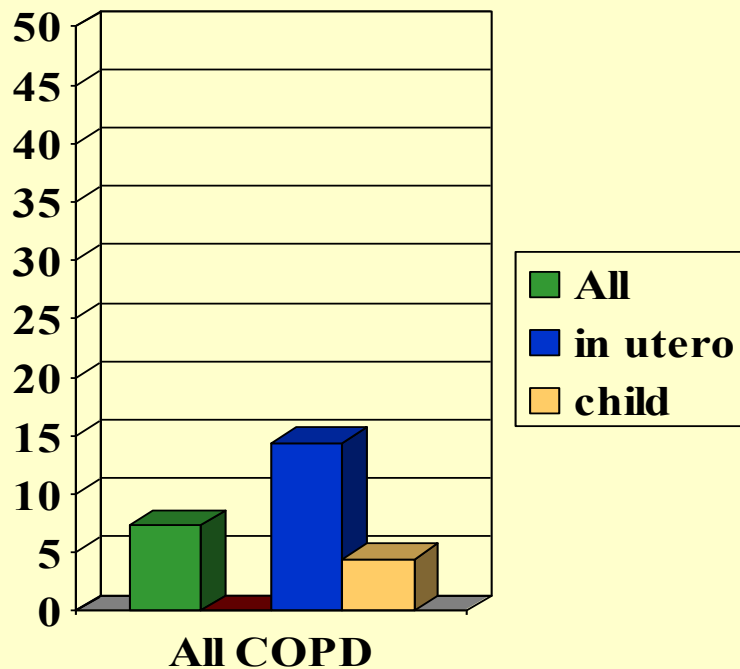
Lung cancer mortality in men according to exposure in childhood

(SMR = standardized mortality ratio = observed/expected deaths)



$p < 0.001$

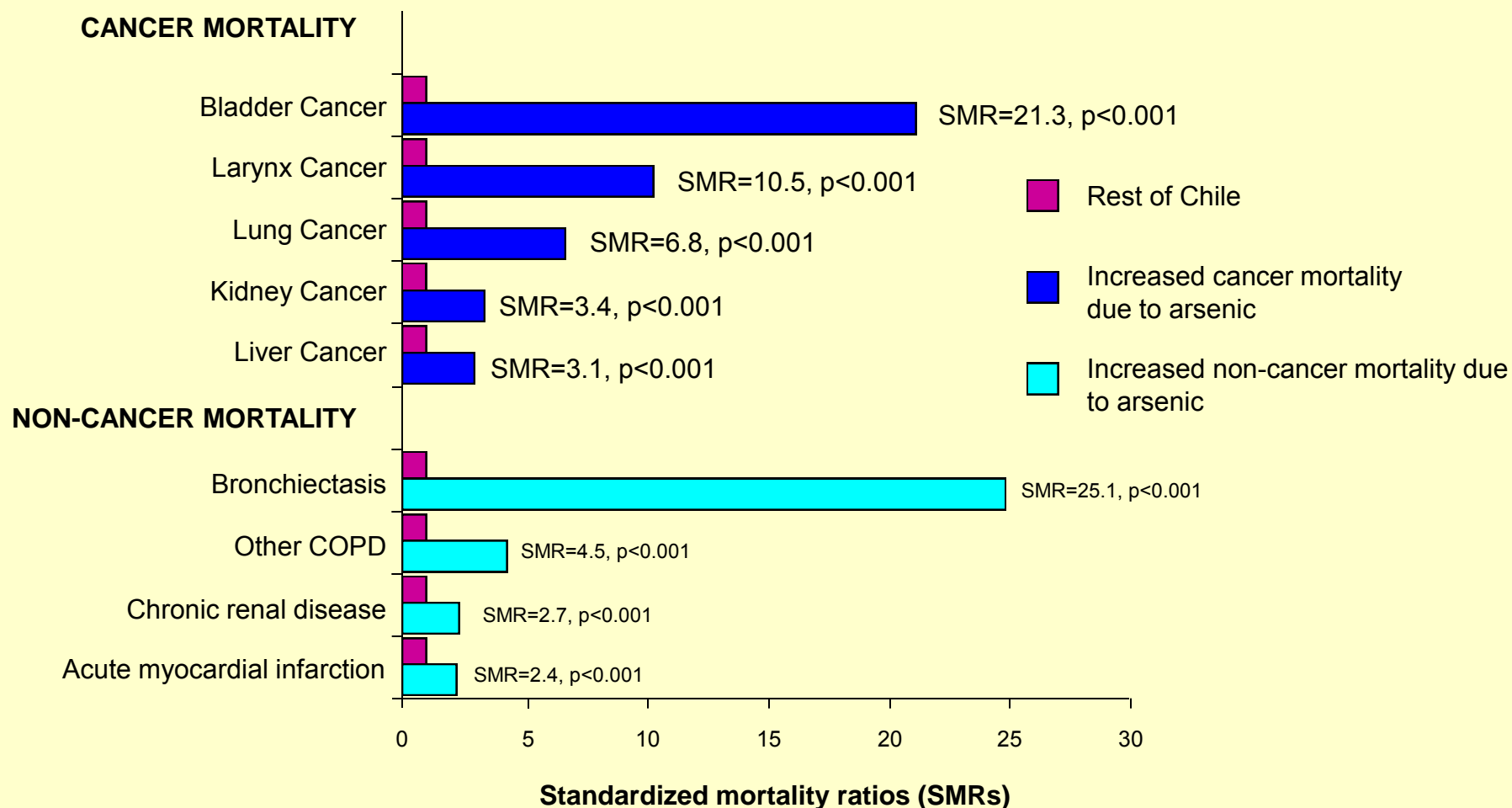
Mortality (SMRs) from Chronic Obstructive Pulmonary Disease, age 30-49, for those born in the very high exposure period (in utero exposure) or just before (child)



$p < 0.001$ except other
COPD $p = 0.004$

Ecologic study of mortality of young adults aged 30-49 following exposure to high concentrations of arsenic in drinking water in early life

(Environmental Health Perspectives, November 2012)



**In 1996 I was asked by WHO to investigate the
newly discovered arsenic in drinking water
problem in Bangladesh**

We subsequently published: Smith AH, Lingas EO and Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. Bulletin World Hlth Org 78:1093-103, 2000.

No. No! Professor Smith. We will not declare it a public health emergency. It might alarm the people.

Studies in other countries where the population has had long-term exposure to arsenic in groundwater indicate that **1 in 10 people who drink water containing 500 mg of arsenic per litre may ultimately die** from cancers caused by arsenic, including lung, bladder and skin cancers.

The rapid allocation of funding and prompt expansion of current interventions to address this contamination should be facilitated.

It was a public health emergency

No. No! Professor Smith. We will not declare it a public health emergency. It might alarm the people.

Relative Risk of Mortality from all nonaccidental deaths in a Bangladesh study (from Sohel N et al, Epidemiology, 2009)

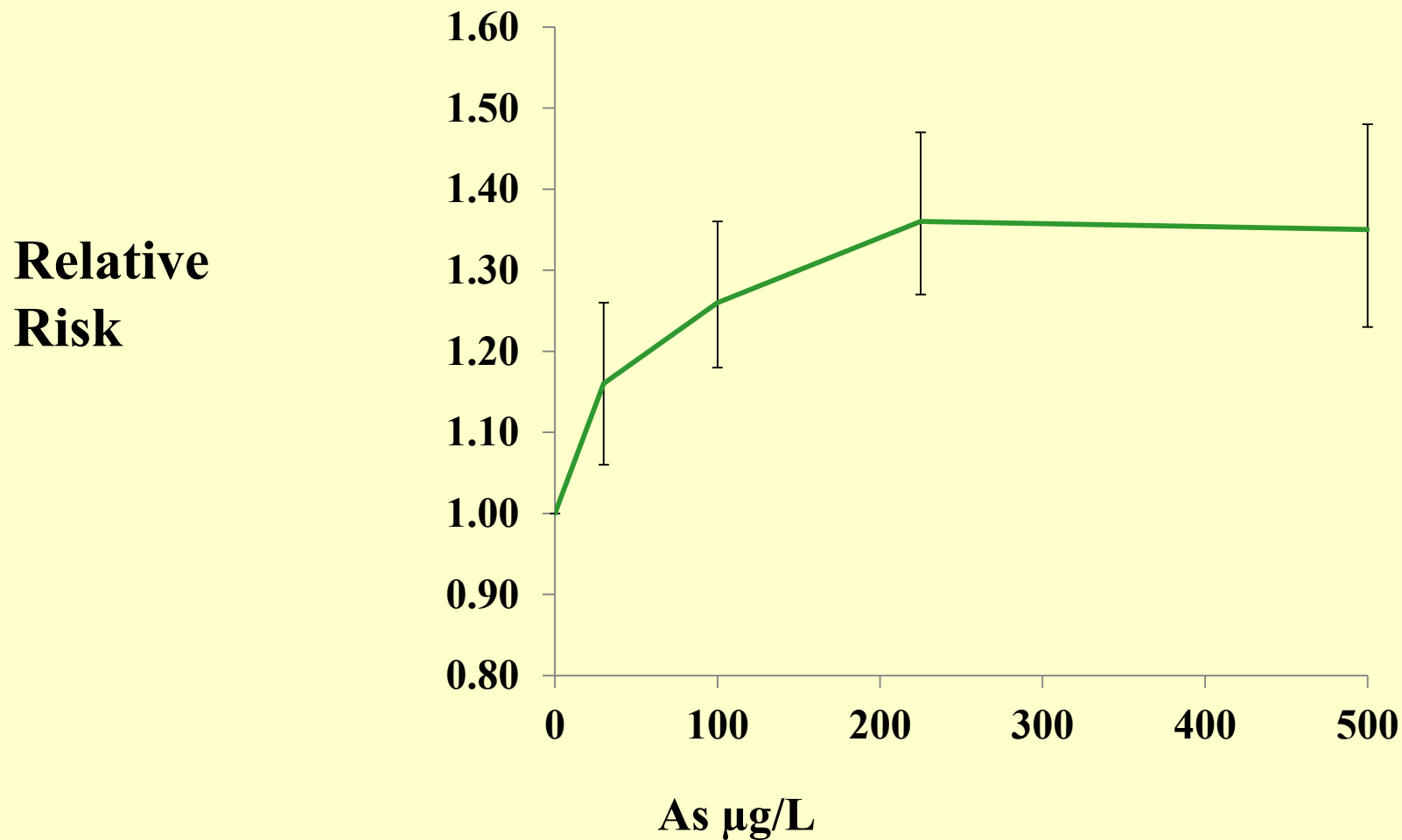
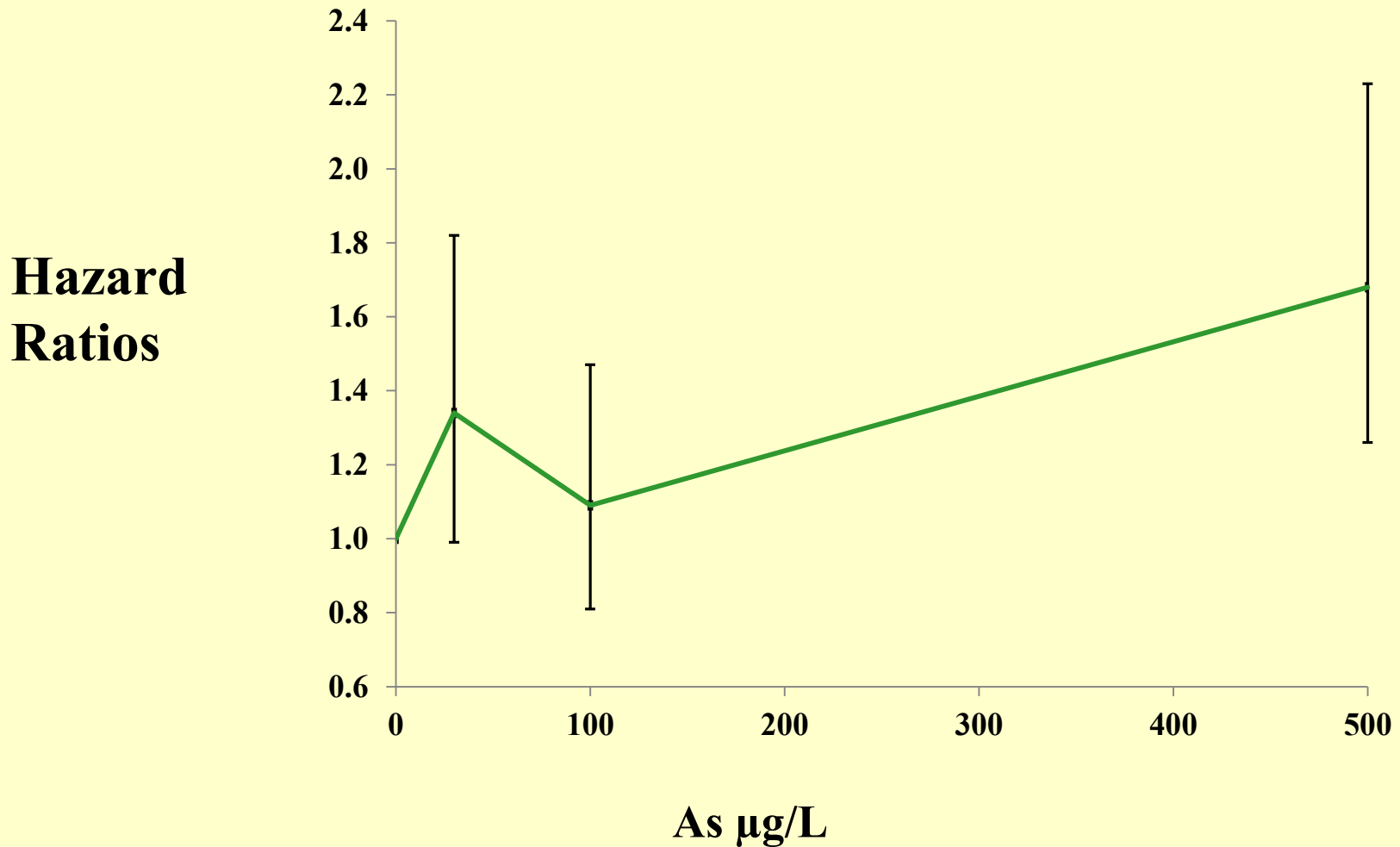


Figure 6: Multivariate adjusted Hazard Ratios for all-cause mortality in a Bangladesh study (from Argos M et al, Lancet, 2010)







Project Well

**Clean drinking water
for West Bengal**

Photography by Rudi Dundas
and Chris Majors

The water crisis is not just about scarcity.
India has a lot of water,
But so much of it we cannot drink...





Project Well has developed an innovative system using PVC pipes to bore up to 27 feet into the earth



80% of all Project Well funds go directly to the villages and the rest goes to our local partner staff.



\$1000 is the cost of a bore-dugwell that will provide drinking water for more than 100 people...



Intervention program in West Bengal

Director: Meera HiraSmith

- Modern design dugwell program to provide arsenic free water in West Bengal
- Funded by private donors
- for more information
<http://www.projectwellusa.org>

First findings concerning arsenic and drinking water and child intellectual function were obtained by Thailand investigators.

Siripitayakunkit U. Association between chronic arsenic exposure and schoolchildren's growth and ability at Ronpiboon District, Nakorn Si Thammarat Province.

abstract. Epidemiology 8:S69, 1997; and also Proceedings of the 3rd International Conference on Arsenic Exposure and Health Effects, San Diego, **1998**

Siripitayakunkit U, Lue S, Choprapawan C. Possible effects of arsenic on visual perception and visual–motor integration of children in Thailand. *Arsenic Exposure and Health Effects IV*, New York: Elsevier; **2001**:165–172

Because of the Thailand findings, in 2000 we were asked by UNICEF to conduct studies of intellectual function in children in West Bengal, India, who were exposed to arsenic in drinking water.

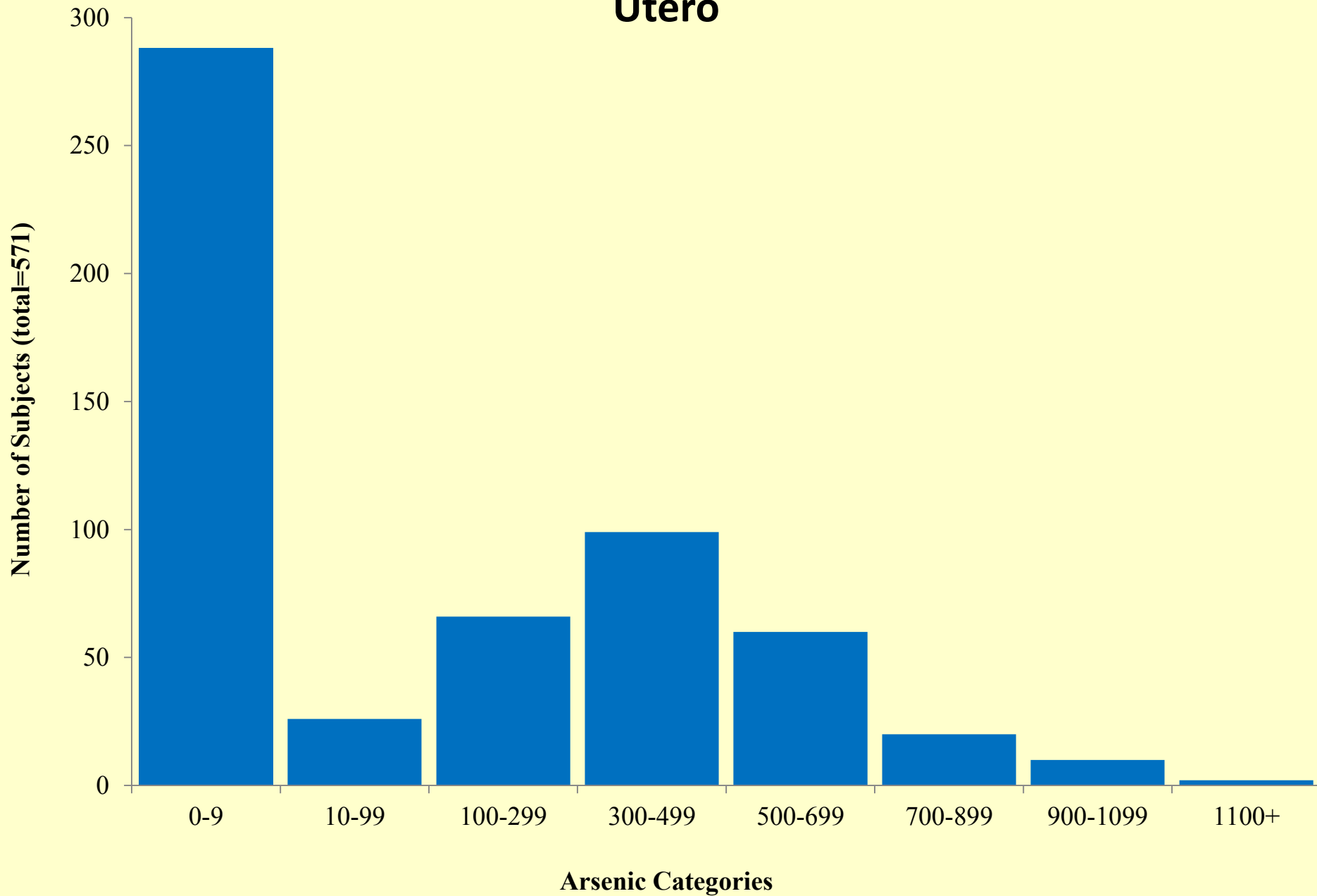
von Ehrenstein et al. Children's intellectual function in relation to arsenic exposure. *Epidemiology* 18:44-51, 2007.

Wasserman GA, Liu X, Parvez F, et al. Water arsenic exposure and children's intellectual function in Araihaazar, Bangladesh. *Environ Health Perspect.* 2004;112:1329–1333.





Distribution of Children's Arsenic Exposure (ug/L) In Utero



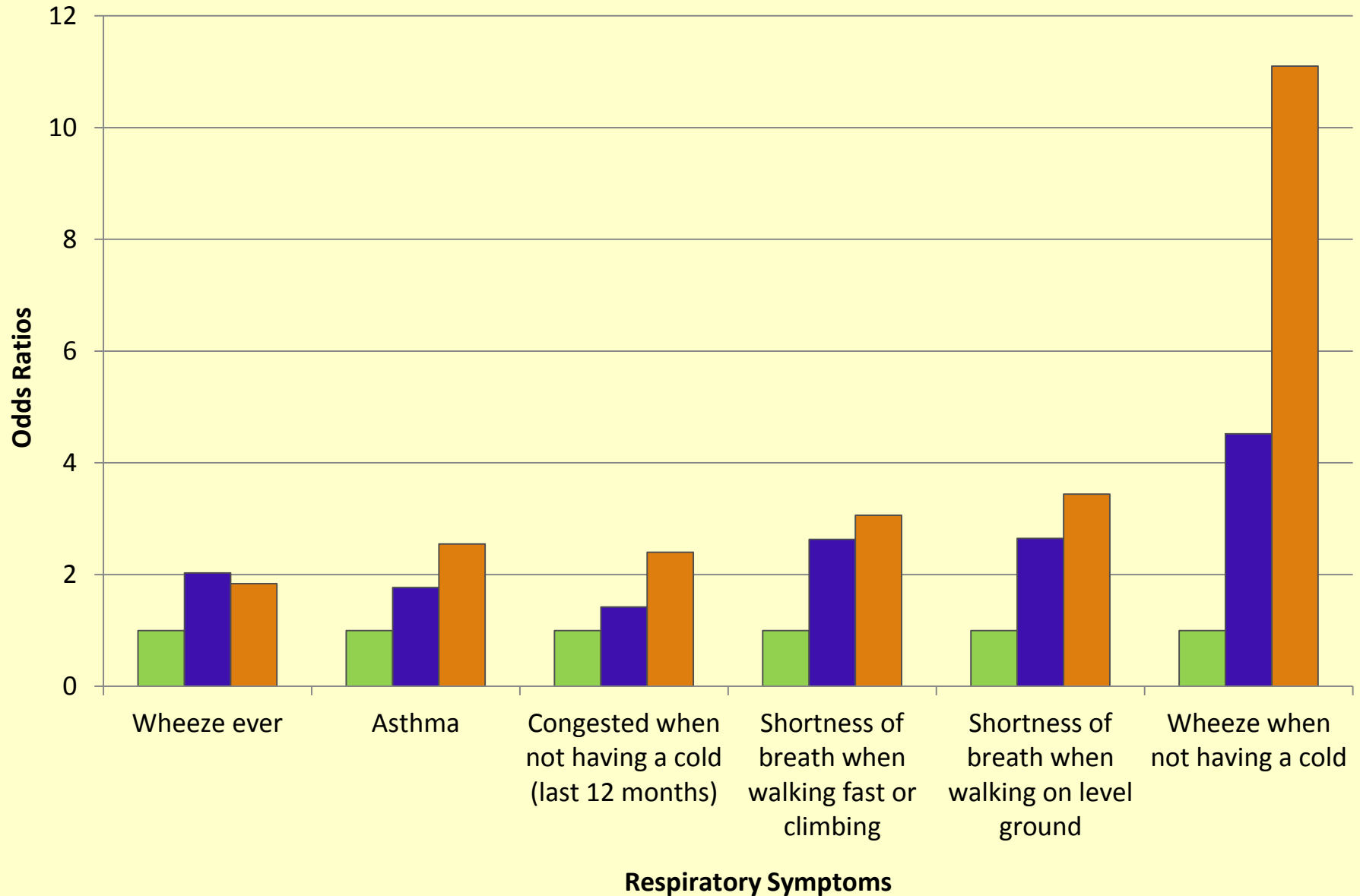
Chronic respiratory symptoms in children following in utero and early life exposure to arsenic in drinking water in Bangladesh

Allan H Smith¹, Mohammad Yunus², Al Fazal Khan², Ayse Ercumen¹, Yan Yuan¹, Meera Hira Smith¹, Jane Liaw¹, John Balmes^{1,3}, Ondine von Ehrenstein^{1,4}, Rubhana Raqib², David Kalman⁵, Dewan S Alam², Kim Streatfield² and Craig Steinmaus^{1,6}

International Journal of Epidemiology 2013, In Press

Respiratory Symptoms for Which Adjusted* Odds Ratios for Highly Exposed Compared with Never Exposed In Utero are Greater Than 2

Never Exposed 10-499 ug/L 500+ ug/L



* Adjusted for age, gender, mother's education, father's education, father's smoking status and rooms in the house

Case-control Study of Arsenic in Drinking Water and Kidney Cancer in Uniquely Exposed Northern Chile

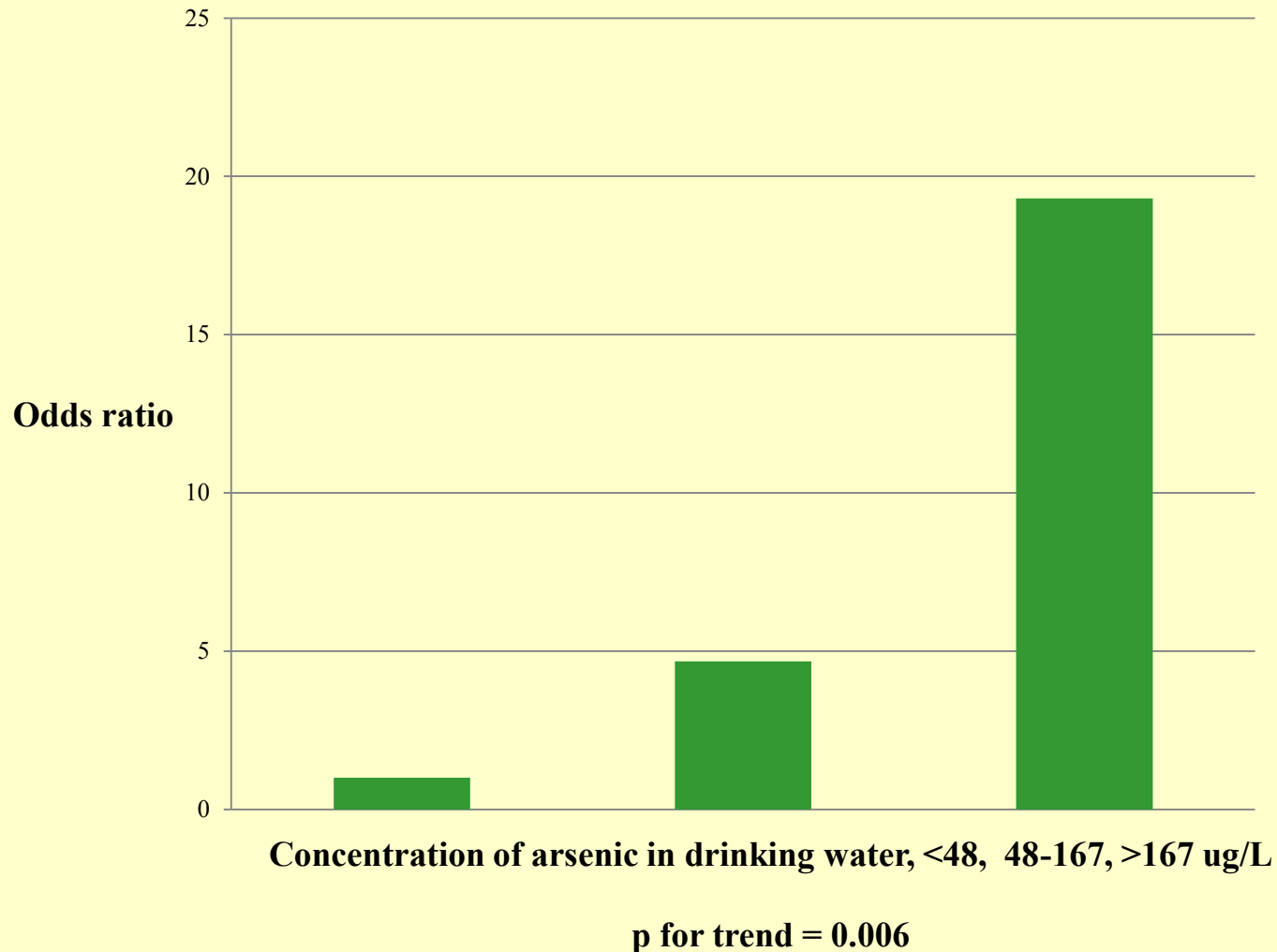
**122 kidney cancer cases and 640 population-based
controls**

Catterina Ferreccio, Allan Smith ... Craig Steinmaus
Am J Epidemiol on- line June 2013

Cases were ascertained from all pathologists and radiologists in the study area, and included people who: 1. had primary kidney or ureter cancer diagnosed between October 2007 and December 2010

Controls without cancer were randomly selected from the Chile Electoral Registry for the study area, frequency matched by gender and five-year age group

Renal pelvis plus ureter cancer odds ratios with increasing arsenic concentrations up to OR=19.3 (95% CI 2.4-154)



Although the IARC has concluded that there is sufficient evidence that arsenic in drinking water causes lung, bladder, and skin cancer, a similar determination has not been made for kidney cancer since “no studies have reported dose-response relationships on the basis of individual exposure data”

With these new findings, including evidence of dose-response, we believe there is now sufficient evidence in humans that drinking-water arsenic causes transitional cell renal pelvis and ureter cancer.

Arsenic, Tobacco Smoke, and Occupation: Associations of Multiple Agents with Lung and Bladder Cancer Risks

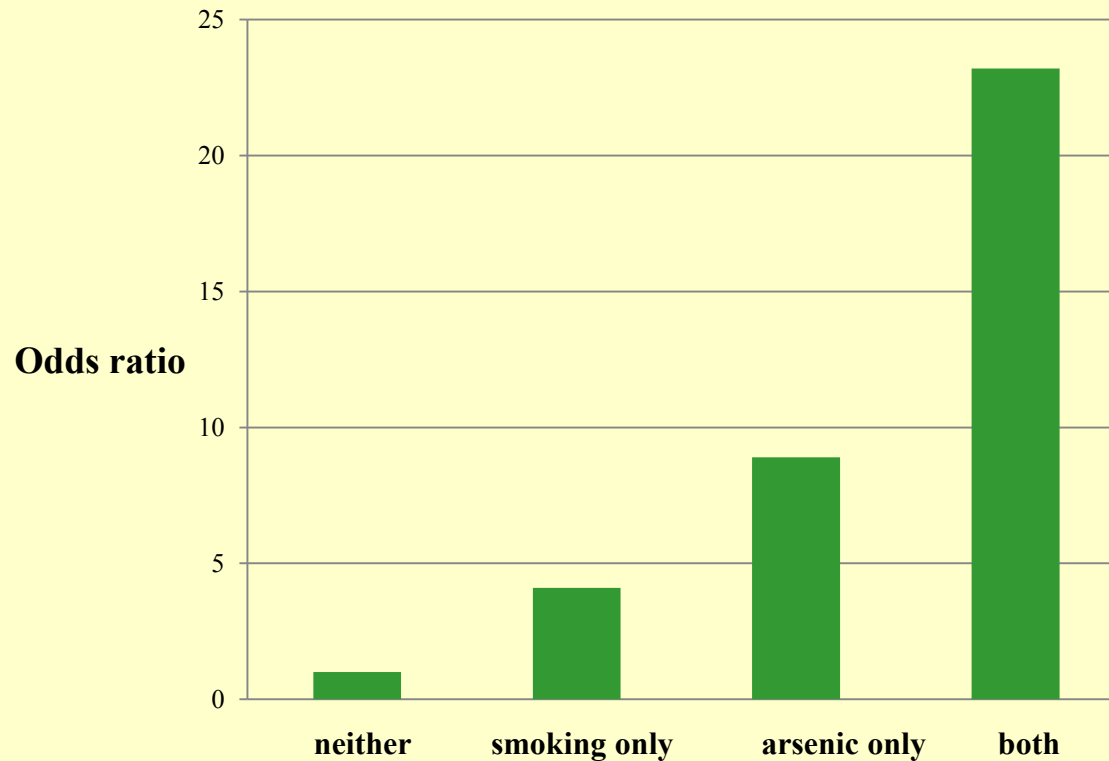
Catterina Ferreccio, Yan Yuan, Jacqueline Calle,
Hugo Benítez, Roxana L Parra, Allan H. Smith,
Jane Liaw, Craig Steinmaus

In Press: Epidemiology

Table 3. Odds Ratios for Bladder Cancer in Relation to Arsenic Concentrations in Water, by Smoking Status, Northern Chile, 2007-2010

	Arsenic < 11 ug/L ^a		Arsenic > 335 ug/L ^a		OR ^b (95% CI) for arsenic within smoking strata
	Cases/ controls	OR ^b (95% CI)	Cases/ controls	OR ^b (95% CI)	
Never smoker	6/79	1.00	19/34	8.86 (2.99-26.23)	8.86 (2.99-26.23)
Smoker	14/45	4.12 (1.30-13.0)	33/18	23.21 (8.15-66.1)	6.20 (2.52-15.25)
OR ^b (95% CI) for smoking within arsenic strata		4.12 (1.30-13.0)		3.20 (1.28-7.97)	

Bladder cancer, synergy of smoking with arsenic going up to OR=23.2 (95% CI 8.2-66)



Latency

Marshall G, Ferreccio C, et al.

Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water.

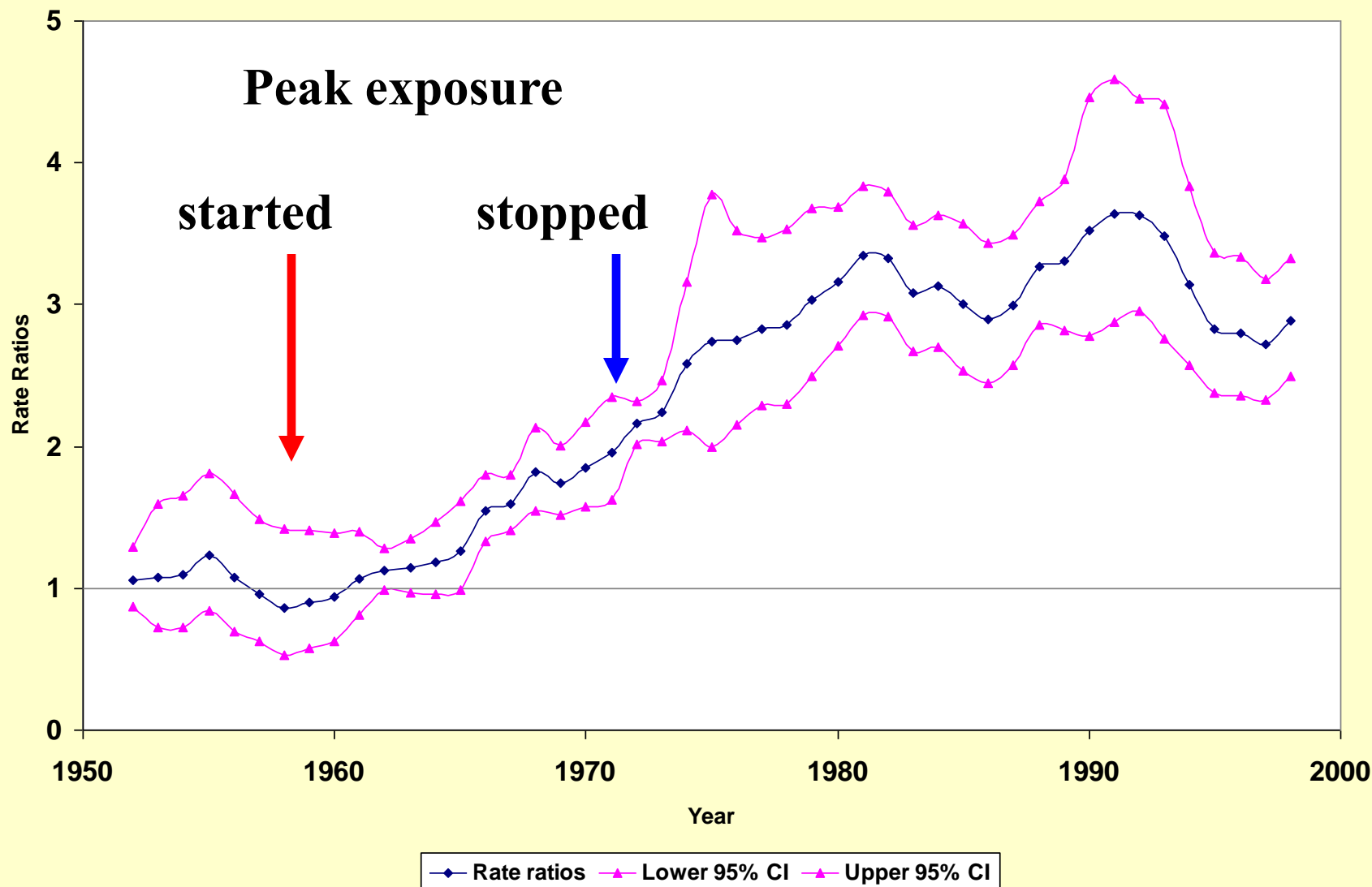


J Natl Cancer Inst 99:920-928, 2007

Mortality data were already available computerized for 1971-2000.

For the years 1950-1971, 200,000 death certificates were digitally photographed and coded for this study.

Mortality from lung cancer among men, Region II Chile Marshall et al, J. Natl Cancer Inst, 2007

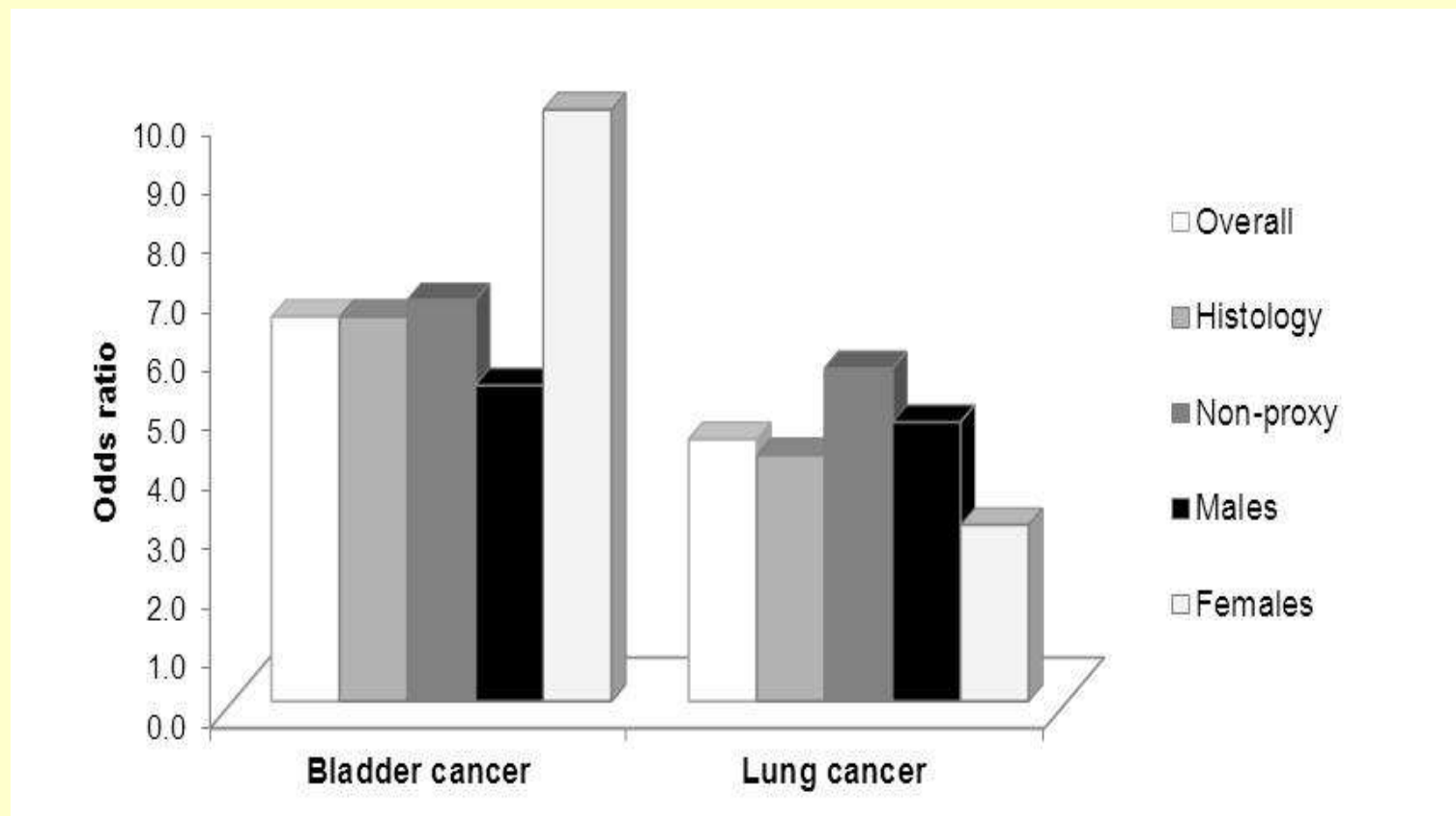


Drinking Water Arsenic in Northern Chile: High Cancer Risks 40 Years after Exposure Cessation

Craig Steinmaus, Catterina Ferreccio, Johanna Acevedo Romo, Yan
Yuan, Sandra Cortes, Guillermo Marshall, Lee E Moore, John R
Balmes, Jane Liaw, Todd Golden, Allan H Smith

Cancer Epidemiol Biomarkers Prev 2013;22:623-630.

Figure 2. Bladder and lung cancer odds ratios* including only cases with histologic confirmation, in non-proxy subjects, and in males and females comparing subjects in the upper to lower quartiles of average lifetime arsenic concentration prior to 1971.



***Odds ratios are adjusted for age, sex, smoking, mining work, race, body-mass index, and socioeconomic status. For display purposes, the bladder cancer odds ratio in females of 23.6 (95% CI, 4.14 to 135.3) is truncated.**

Drinking Water Arsenic in Northern Chile: High Cancer Risks 40 Years after Exposure Cessation

Bladder and lung cancer odds ratios in those highly exposed in Antofagasta during 1958-70 but not thereafter were 6.88 (3.84 to 12.32) and 4.35 (2.57 to 7.36), respectively.

$p < 0.001$

The only other known cause of cancer with a long latency like this after cessation of exposure is between asbestos and mesothelioma

So what do we now think arsenic in drinking water causes?

- Respiratory Cancers of the lung and larynx, reduced lung function, bronchiectasis, chronic cough and shortness of breath.
Tuberculosis mortality increased?
- Renal tract Bladder and kidney cancer, chronic renal failure
- Cardiovascular Myocardial infarction, cerebrovascular effects, hypertension.
- Neurological Peripheral neuropathy, reduced cognitive function in children
- Other Skin pigmentation changes, skin cancer, liver cancer, diabetes

*Once we asked what arsenic might cause;
now we ask, what does it not cause?*