TABLE III

HIGGINS LIFETIME CEILING
AND RESULTS FOR SAMPLE STUDY OF ANACONDA SMELTERMEN+

Category	Exposure Estimates - 8 hr TWA		Respiratory Cancer Mortality Risk	
	Average	Range of Measurements	O/E	SMR
Very High (>5,000 ug/m^3)	11,892 ug/m^3	(6,870-20,060)	34/5.5	617*
High (500-4999 ug/m^3)	1,387 ug/m^3	(598-2,589)	41/13.7	300*
Medium (100-499 ug/m^3)	255 ug/m^3	(111-415)	2/2.4	82
Light (<100 ug/m^3)	43 ug/m^3	(0.45-82)	3/3.9	77

+ Higgins et. al., 1982 (11)
* p <.01

Figure 5 shows that for the whole group reported by Higgins, the excess risk appears to increase rather linearly with increasing cumulative exposure. However, Figure 6 illustrates that this risk is essentially that of workers with ceiling exposures above 500 $\mu g/m^3$. On the contrary, Figure 7, which represents the mortality experience of workers whose 30 day ceiling exposures did not exceed 500 $\mu g/m^3$, shows no increased risk for workers with cumulative exposures up to 12,000 $\mu g/m^3$ - years.

The critical fact for quantitative risk assessment purposes is that workers with exposures below 500 $\mu g/m^3$ evidenced lower than expected mortality overall, and in all but the highest cumulative exposure group. The elevated SMR in the highest cumulative exposure category is determined by one case (with 0.1 expected): a man who was hired in 1903, worked for 16 years in low exposure jobs and then worked for 31.5 years in the tram (a department with an assigned exposure level of 415 $\mu g/m^3$, based on measurements from the 1950s).[12] During the course of this employment, it is very likely that this worker had exposures to levels well above 500 $\mu g/m^3$ for sustained periods. This analysis supports the observation that workers without exposures near or above 500 $\mu g/m^3$ do not experience excess lung cancer risk.

The foregoing analyses of the Higgins data suggest that exposure intensity appears to be the critical determinant of respiratory cancer risk and that exposures below 500 $\mu g/m^3$ are not associated with excess risk. This result (see Figure 4) is consistent with a non-linear "hockey-stick" or threshold model.[13]

The differences in the exposure assignments and classification system used by Higgins and by NCI may account for the very marked difference in the interpretive results for these studies. Risk assessments based upon the NCI classifications predicted excess lung

TABLE IV

COMPARISON OF HIGGINS ET AL. AND LEE-FELDSTEIN DEPARTMENTS BY EXPOSURE CATEGORY

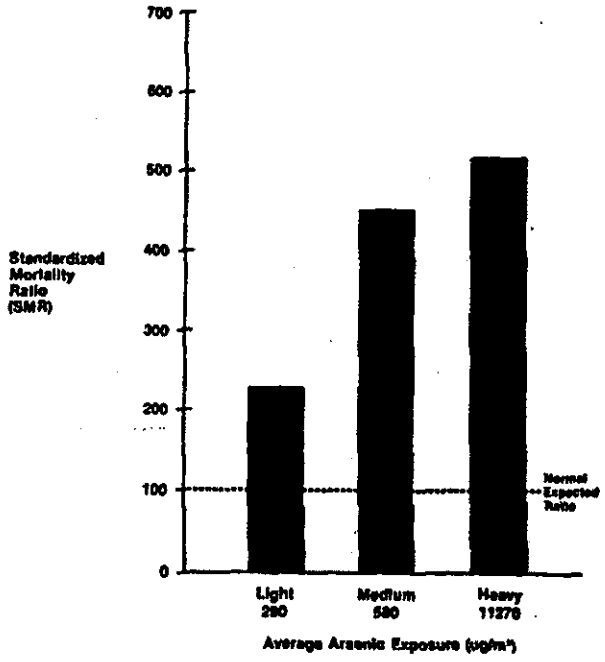
NCI GROUPINGS		HIGGINS GROUPINGS			
Group	Exposure (ug/m³)	Very High (5000+)	High (500-4999)	Medium (100-499)	Low (<100)
Heavy	11270	Arsenic Roaster* Arsenic Refinery* Cottrells* Main Flue*			
Medium	500		Ore Roaster* (excluding acid plant) Reverberatory Furnace* (excluding slag workers)	Converter*	Casting* Acid Plant*
Light	290		Maintenance Surface Shops Unknown Masons* Slag	Zinc Roaster* Zinc Plant	Concentrator Ferromanganese Plant* Foundry Lead Plant Lime Processing General Office Phosphate Plant* Engineering Power Research+ Plant Office Brick Yard Industrial Hygiene+ Company Farm Coal* Lab Sample Mill**
Reclassified[2]			Materials Crushing* Rag House Electric Furnace	Train*	Area 21

*Denotes Departments with actual exposure measurements from Higgins. There is no information about the measurements used in the NCI classifications scheme.

+Made into a separate department by Higgins

[13]Morris, H.F., 1975 (6)

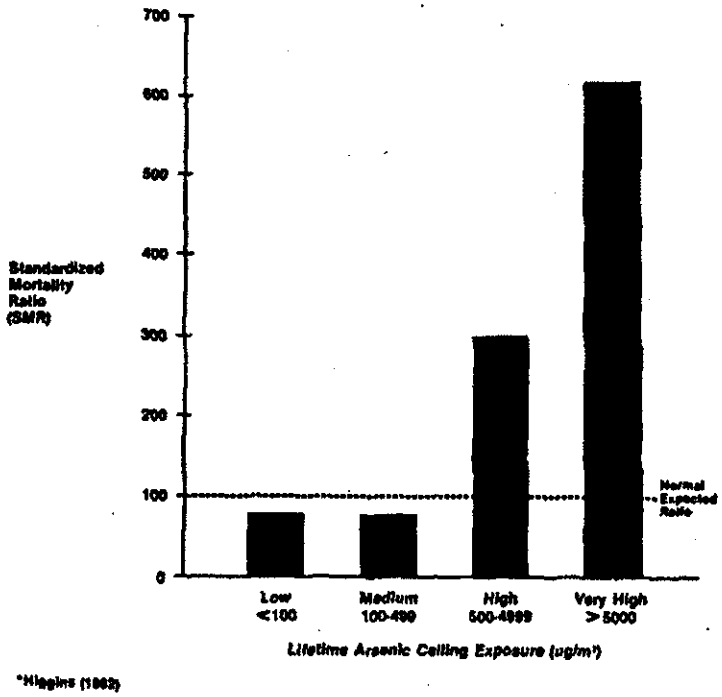
**Departments newly identified by Higgins in areas considered by Lee-Feldstein to have neither medium nor heavy exposures.



*Lee-Feldstein (1983)

Figure 3

Lung Cancer Mortality by NCI Exposure Category*



*Higgins (1982)

Figure 4

Lung Cancer Mortality by Higgins et al. Exposure Category*

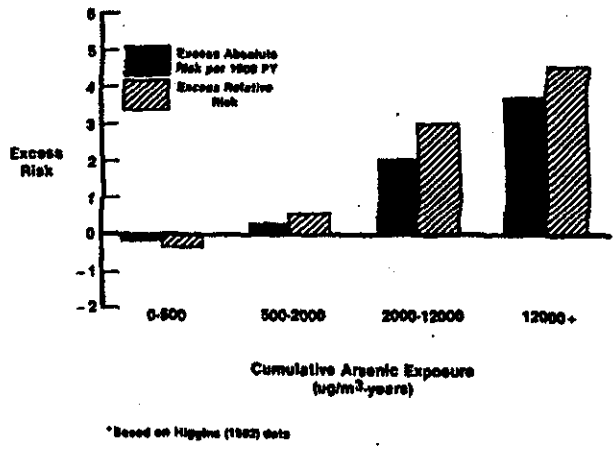


Figure 5

Respiratory Cancer Risks by Cumulative Exposures for Workers with Lifetime Ceiling Exposure Levels of 500 $\mu g/m^3$ or Greater or of Less than 500 $\mu g/m^3$*

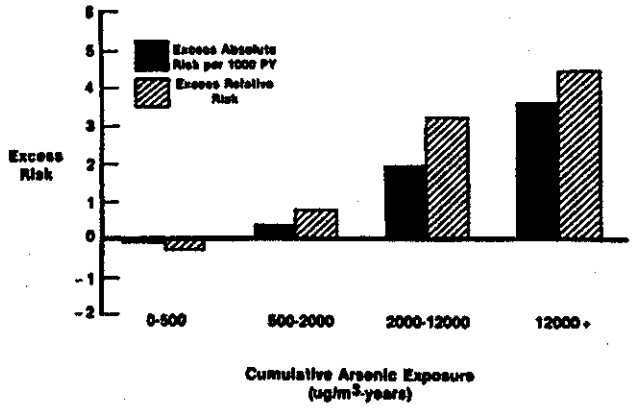


Figure 6

Respiratory Cancer Risks by Cumulative Exposures for Workers with Lifetime Ceiling Exposure Levels of 500 $\mu g/m^3$ or Greater*

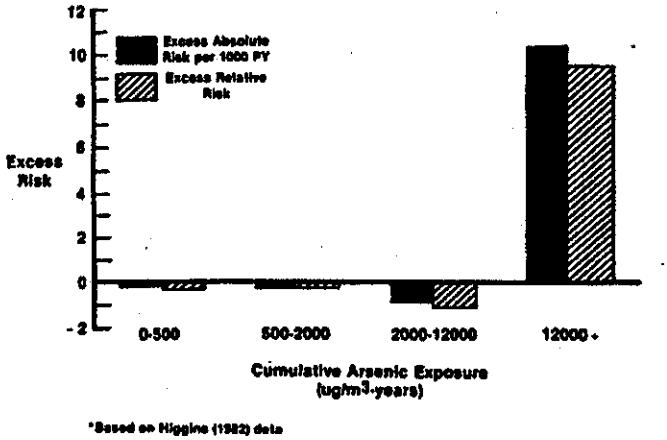


Figure 7

Respiratory Cancer risks by Cumulative Exposures for Workers with Lifetime Ceiling Expousre Levels of less than 500 $\mu g/m^3$

cancer risk at low arsenic exposure levels (0-500 $\mu g/m^3$). However, analysis using the Higgins classification, on the contrary, strongly suggests that exposures to airborne inorganic arsenic at levels below 500 $\mu g/m^3$ are not associated with excess respiratory cancer risk.

These data suggest that a threshold exposure level may exist below which respiratory cancer risk is not increased. Because of their more precise quantitative exposure descriptions, the Higgins exposure classifications may be better suited than the NCI groupings for quantitative risk assessment at low exposure levels. The differences illustrate the need for careful attention to exposure description and quantification that is necessary to perform quantitative risk assessment. This current analysis of ours is based on only a few observed lung cancer cases in the group whose exposures remained below 500 $\mu g/m^3$ (Table V). Higgins is currently expanding his study to the entire Anaconda cohort and updating the mortality followup to 1980. The results of the larger extended study should serve well to test the hypothesis that we have developed based on observations from his initial study, namely that there appears to be a carcinogenic threshold for arsenic exposure approximating 500 $\mu g/m^3$.

TABLE V

CUMULATIVE LIFETIME ARSENIC EXPOSURE (g/m^3-yrs)*

	<500	500-2,000	2,000-12,000	>12,000
Exposures <500 ug/m³				
Lung Cancer Cases	3	1	0	1
Expected Cases	4.5	1.3	0.5	0.1
Person-Years Obs.	9002	1589	563	87
Exposures >500 ug/m³				
Lung Cancer Cases	1	8	27	39
Expected Cases	1.3	4.5	6.4	7.2
Person-Years Obs.	4934	9304	10656	8931

* Data from Higgins et al. presented at OSHA Arsenic Hearing (1982) by Lamm

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M. Luann Roegner · Karen S. Grumski ·

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Daniel M. Byrd · James C. Griffiths · Steven H. Lamm
Richard Wilson · Shenghan Lai

Carcinogenic risks of inorganic arsenic in perspective

Abstract Induction of cancer by inorganic arsenic occurs inconsistently between species and between routes of exposure, and it exhibits different dose-response relationships between different target organs. Inhaled or ingested arsenic causes cancer in humans but not in other species Inhaled arsenic primarily induces lung cancer whereas ingested arsenic induces cancer at multiple sites including the skin and various other organs. Cancer potency appears to vary by route of exposure (ingestion or inhalation) and by organ site and increases markedly at higher exposures in some instances. To understand what might explain these inconsistencies, we reviewed several hypotheses about the mechanism of cancer induction by arsenic. Arsenic disposition does not provide satisfactory explanations. Induction of cell proliferation by arsenic is a mechanism of carcinogenesis that is biologically plausible and compatible with differential effects for species or differential dose rates for organ sites. The presence of other carcinogens, or risk modifiers, at levels that correlate with arsenic in drinking water supplies, may be a factor in all three inconsistencies: interspecies specificity, organ sensitivity to route of administration, and organ sensitivity to dose rate.

Work presented at the "23rd Congress on Occupational and Environmental Health in the Chemical Industry" (MEDICHEM 1995) "The Chemical Industry as a Global Citizen – Balancing Risks and Benefits", 19–22 September 1995, Massachusetts Institute of Technology, Cambridge Massachusetts

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Introduction

At present, the scientific consensus is that arsenic ingestion causes human skin cancer [1] and that arsenic inhalation causes human lung cancer [2], but neither route of exposure causes cancer in other species [3, 4]. Inhaled arsenic primarily induces lung cancer, whereas ingested arsenic notably induces skin cancer but also is associated with leukemias and cancers of the bladder, lung, kidney, gastrointestinal tract, liver, and other organs [5]. Because inhaled arsenic is absorbed into the general circulation, distributed, metabolized, and eliminated through urine [6], the relative absence of leukemias or cancers at sites such as skin, bladder, and kidney after inhalation appears to contradict the ingestion data.

Studies of drinking water supplies with high arsenic levels in India, Japan, Mexico, Inner Mongolia, and South America have extended the general observations of an association between ingestion and skin cancer [7, 8, 9, 10, 11]. Many studies of arsenic ingestion lack quantitative exposure data, however, so that quantitative evaluations of ingested arsenic as a skin carcinogen usually depend on a single report by W.P. Tseng and coworkers [12].

Tseng studied an area in Southwestern Taiwan with well water as the primary source of drinking water. Many of these wells had high concentrations of arsenic. Residents had a high incidence of several diseases, most no-

tably Blackfoot disease, a vascular occlusion of the extremities, and dermatological conditions, including skin cancer. Prevalence correlated with dose rate of arsenic and with age, which was a surrogate measure of duration of exposure, because of lifetime exposure [12]. Professor Chien-Jen Chen and his coworkers later augmented Tseng's observations by expanding the cohort size and by studying other diseases, including goiter and hepatitis B, in the same cohort [13, 14, 15]. Through detailed studies of death certificates, they found that the mortalities from liver, kidney, and bladder, and even lung cancer, also correlated with arsenic dose rate and duration of exposure [16].

The lung cancer potency of inhaled arsenic appears to increase with dose rate [2]. In this paper we similarly analyze the dose rate dependence for skin cancer potency of ingested arsenic, using the Tseng data, and review potential explanations for apparent inconsistencies in interspecies sensitivity to arsenic, organ sensitivity to route of exposure, and organ sensitivity to dose rate.

Methods of analysis

We identified all data from the published scientific literature that quantitatively relate skin cancer prevalence to arsenic ingestion [9, 11, 12, 17, 18, 19, 20, 21] and applied several modeling approaches. The terms in the models are defined as follows:

y = prevalence, f = some function, D = dose rate, D_g = a fixed dose rate (> 0), and $q_0, q_1, q_2, \ldots q_n$ = constants (unknown parameters).

Linear models

$$y = q_0 + q_1 D \quad (q_0 \geq 0,\ q_1 \geq 0)$$

A linear processes reflects direct proportionality; i.e. the increase in prevalence for an incremental increase in dose is constant over all dose rates.

Segmented linear models

$y = q_0 + q_1 D$, if $0 \leq D \leq D_g$, and
$q_0 + q_1 D + q_2(D - D_g)$, if $D \geq D_g$,
where D_g is a fixed dose, $D_g > 0$ and $q_0 \geq 0$, $q_1 \geq 0$, and $q_2 \geq 0$.

A segmented linear model describes a combination of two direct proportionality processes, at least one of which has no threshold. These models can easily be extended to more than two processes. This model describes a biological mechanism in which different, independent, concurrent processes act to increase prevalence, but some of these processes do not contribute until some level of exposure is reached.

Truncated polynomial fit models

Another possibility is to expand the parameter y into a power series in dose. These models sometimes are described as truncated polynomial fit models. A modification must be made to account for the fact that no one dies more than once. The formula becomes

$$y = 1 - e^{-(q_0 + q_1 D + q_2 D^2 \ldots + q_n D^n)},$$

where n is constrained to one less than the observed number of doses, because of the limited degrees of freedom. We used MSTAGE, a modified power law expansion model created by Dr. Edmund Crouch to calculate power law expansion models and the various multistage models described below. The error bars in the figures describe the statistical uncertainty that is attributable to the number of persons with cancer (or cancer fatalities).

Multistage models

Multistage models are biological models, often attributed to Armitage and Doll [22], although many other persons contributed to their earlier development. Multistage models arise by assuming that there are a number of sequential biological steps, each requiring time, that must take place before a cancer develops. Several variants of the multistage model are identical to truncated polynomial fit models, as above, but with positive coefficients for each term in the power series. This constraint leads to a response that increases in a strictly monotonic way as a function of increasing dose.

Linearized multistage models

The form of the linearized multistage preferred by the U.S. Environmental Protection Agency (EPA) uses a truncated polynomial fit model with an upper limit in some statistical sense on the coefficient of the linear slope (dose term q_1) with the other coefficients held constant [23, 24].

We follow this procedure with the Mstage program but allow the other coefficients to vary to obtain the best fit overall.

Results

The eight studies of arsenic ingestion we found in the literature (Table 1) yield a dose-response relationship for skin cancer induction in which prevalence increases with dose rate (Table 2, Fig. 8). The risk of skin cancer appears non-linearly related to arsenic dose rate, perhaps with a discontinuity or threshold in the range from approximately 100 to 200 ppb. Within the overall data, the origi-

Table 1 Studies on ingested arsenic and skin cancer

Author	Year	Place	Exposure	Dose levels	Pop.	Cancers
Fierz	1965		Fowler's Solution	?	262	21
Tseng	1968	Taiwan	Well Water	4	47,921	428
Goldsmith	1972	California	Well Water	1	92	0
Zalvidar	1974	Chile	Water	1	?	?
Tay	1975	Singapore	Herbal Medicines	?	74	6
Harrington	1978	Alaska	Well Water	1	211	0
Cebrian	1983	Mexico	Water	2	614	4
Southwick	1979	Utah	Well Water	1	250	0

Table 2 Dose-response data from studies of arsenic ingestion Fig. 1 plots these data

Author	Year	Dose rate (ppb)	Population	Cancers	Prevalence (%)
Tseng	1968	785	8251	185	2.20
Tseng	1968	473	5413	60	1.10
Cebrian	1983	410	296	4	1.40
Harrington	1978	224	211	0	0.00
Southwick	1979	200	250	0	0.00
Tseng	1968	171	9526	21	0.20
Goldsmith	1972	120	92	0	0.00
Tseng	1968	5	7500	0	0.00
Cebrian	1983	5	318	0	0.00

Table 3 Sample weighted means for exposure intervals in the study of Tseng et al. [12]

	D (ppb)	Mid-point	Wtd mean
Low dose	0–300	150	171
Medium dose	300–600	450	473
High dose	> 600	1200	785

nal data from Tseng [12] are consistent with the overall data and have the largest population size. These exposure data are ecological averages rather than individual exposures (Table 3).

The assignment of dose (or dose rate) is a crucial step in modeling. In this paper the concentration of arsenic in well water serves as a surrogate for dose rate. The preferred approach would use population weighted means. In the absence of data that allow the calculation of population weighted means, we used sample weighted means with mid-ranges for closed exposure intervals and an approximation for the first quartile, which is in an open exposure interval, because its lower bound is not zero but is unknown. Table 3 describes the application of this strategy to the arsenic levels in well water and skin cancer prevalence in Tseng's study [12].

Because of the discontinuity in the dose-response relationship, any linear model will fit Tseng's data poorly (Fig. 1). The error bars in Figure 1 represent one standard deviation. Alternatively, it is possible to fit Tseng's data with a single straight line and a threshold. Assuming a threshold at 100 ppb, a slope of $3.14 \times 10^{-5} \times D$ provides a best fit to the data with a correlation coefficient of approximately 0.9. A segmented linear model of the data improves on this fit. We obtained a segmented linear model with two successive slopes of $9.2 \times 10^{-6} \times D$ and $2.2 \times 10^{-5} \times (D-143)$, in units of case prevalence rate per ppb arsenic in drinking water (ppb^{-1}).

We initially hoped to link each of these two slopes to underlying biological process but could not find adequate experimental data to justify such a procedure. There is a problem in extracting two linear relationships from a data set with only four data points. Because of limitations on the available degrees of freedom, it is not possible to tell if, for example, three independent process might be involved. Our efforts to separate these slopes using a statistical justification, through regression on a segmented linear model, failed. Slightly different, but reasonable, approaches to estimate the first slope, generated a variety of thresholds between 100 to 200 ppb. Lacking a biological justification at present for two independent processes, we reserved investigation of segmented linear models for later research.

Unlike the linear or segmented linear models, which only utilize dose rate as the explanatory variable, the multistage model permits consideration of age or duration of exposure, because model coefficients represent the times for events to occur. Since lifetime exposure to well water occurred within Tseng's cohort, age is a measure of duration of exposure. Tseng's paper provides age data both as age intervals, assuming a maximum age of 100 years, and as lifetime exposures, assuming a 76 year mean lifetime. We recalculated age-specific skin cancer prevalence rates

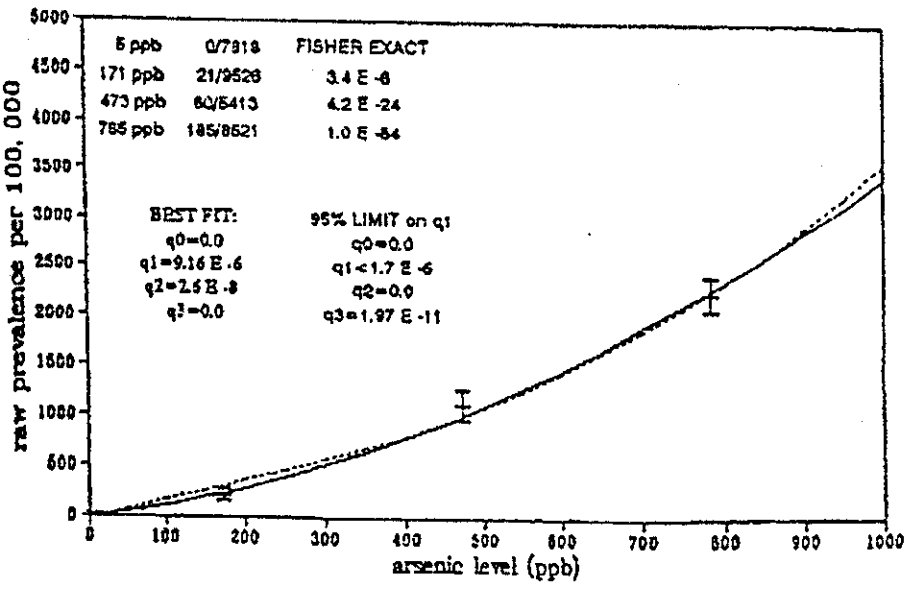

Fig. 1 Multistage model of overall skin cancer prevalence as a function of arsenic dose rate in the study by Tseng and coworkers [12]. —— best fit, ---- 95% limit on q1

Table 4 Drinking water arsenic levels and skin cancer prevalence in the study by Tseng et al. [12]

Exposure level	As dose rate (ppb)	Population	Cases	Prevalence (%)
Background	5	7,500	0	0.00
Low exposure	171	9,526	21	0.22
Medium exposure	473	5,413	60	1.11
High exposure	785	8,251	185	2.24

from these data, as shown in Table 4. We assume that the age dependence of prevalence and the time dependence of prevalence are approximately separable.

The time distribution of skin cancer prevalence is shown in Table 5. The rate of change in prevalence with age in this information describes a process in which prevalence increases with the fourth power of age. From these data we also estimated a cumulative lifetime risk (0.157), which resembles the risk for the elderly (0.103), an order of magnitude greater than the hypothetical average risk (0.0108). These data demonstrate that the skin cancer prevalence risk in Tseng's cohort was markedly age (or duration) dependent. This nonlinear relationship is best approximated as a carcinogenic process with four stages. Fig. 1 illustrates the overall prevalence of skin cancer as a function of dose rate.

We used the subsequent data on mortality [16] and arsenic levels in well water measured during 1964–1966 [12], to analyze internal organ cancers. Arsenic levels ranged from 10 to 1,750 ppb with two clusters at 50 to 250 ppb and 450 to 650 ppb. Chen and coworkers classified villages by median arsenic levels of well water and categorized exposures into three groups, corresponding to those used by Tseng: less than 300 ppb, 300 to 590 ppb, and above 600 ppb.

To calculate multistage models, we took the number of cancers observed as the outcome numerator, R, and the number of cases expected, N, as the denominator, per unit of time, such that R/N was the rate. Figures 2 and 3 display the data and models for fatal skin cancer cases in males and females respectively. Because mortality was approximately 10% of prevalence for skin cancer, the number of cases in these figures are lower than in Fig. 1. Although statistical accuracy decreased, there is general agreement with the nonlinearity of skin cancer prevalence with arsenic dose rate. Arsenic apparently has lower potency in inducing skin cancer at low dose rates than at high dose rates. Figures 4 and 5 show the data and models for fatal kidney cancer cases in males and females respectively, and Figs. 6 and 7 show the data and models for fatal bladder cancer cases in males and females respectively. Despite the small numbers of cases, only small differences were found between the linearized and best fitting multistage models, with a best fit and with the upper 95th percentile for the linear term. In contrast to the findings for skin cancer, the internal cancer cases exhibit a directly proportional relationship with arsenic dose rate, except for female kidney cancers, and even these have less curvature than the female skin cancer cases.

Table 5 Time distribution of skin cancer prevalence in Taiwanese cohort

Age	0–19	20–39	40–59	60+	Lifetime	Average
t (years)	10	30	50	70	76[a]	40[b]
ln (t)	2.3	3.4	3.9	4.25	4.33	3.7
Cases	0	31	197	208	–	436
Persons at risk	22,813	9,527	6,146	2,020	–	40,506
y = prevalence	< 0.00013	0.00325	0.032	0.103	0.157[b]	0.0108

[a] = hypothetical; [b] = calculated

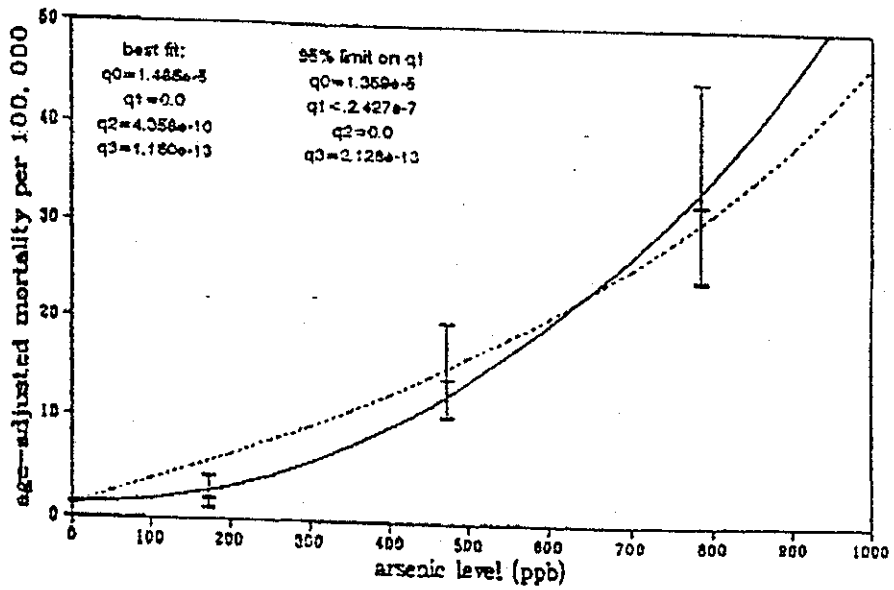

Fig. 2 Multistage model of male skin cancer mortality as a function of arsenic dose rate in the study by Wu and coworkers [16]. —— best fit, ----- 95% limit on q1

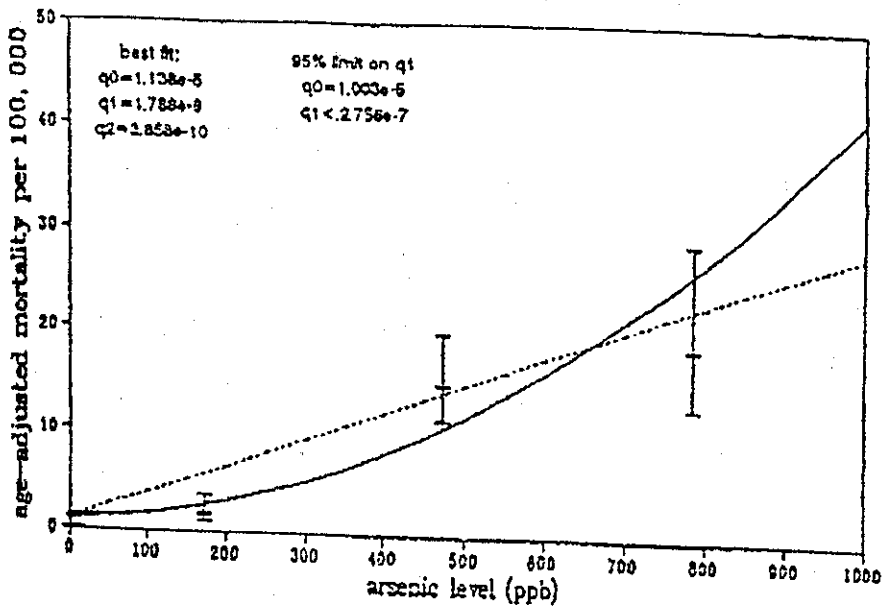

Fig. 3 Multistage model of female fatal skin cancers as a function of arsenic dose rate in the study by Wu and coworkers [16]. —— best fit, ----- 95% limit on q1

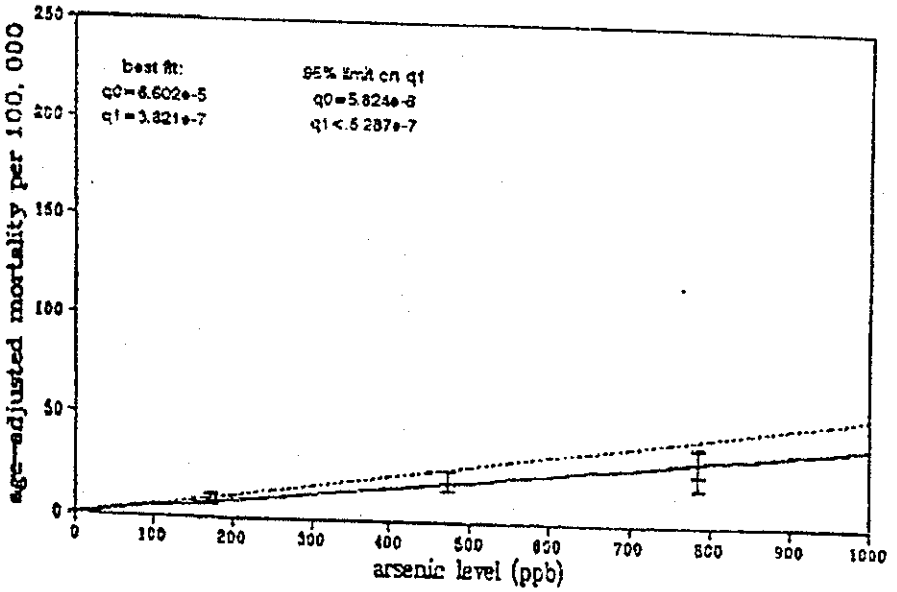

Fig. 4 Multistage model of male fatal kidney cancers as a function of arsenic dose rate in the study by Wu and coworkers [16]. —— best fit, ----- 95% limit on q1

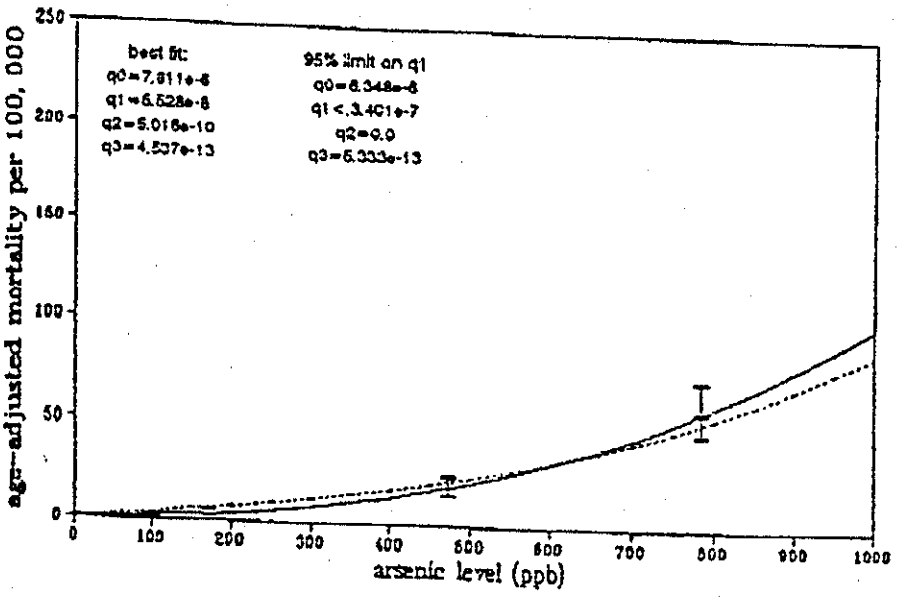

Fig. 5 Multistage model of female fatal kidney cancers as a function of arsenic dose rate in the study by Wu and coworkers [16]. —— best fit, ----- 95% limit on q1

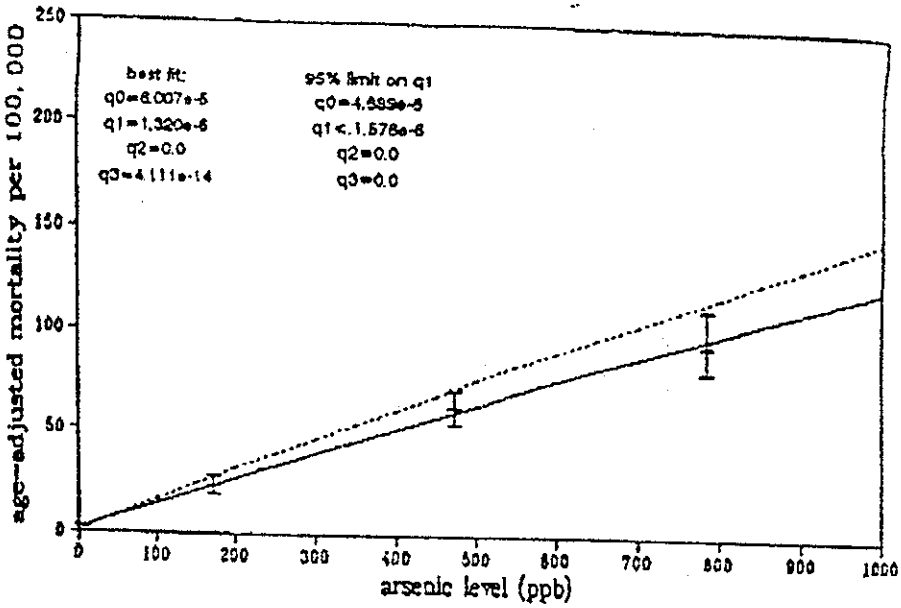

Fig. 6 Multistage model of male fatal bladder cancers as a function of arsenic dose rate in the study by Wu and co-workers [16]. —— best fit, ----- 95% limit on q1

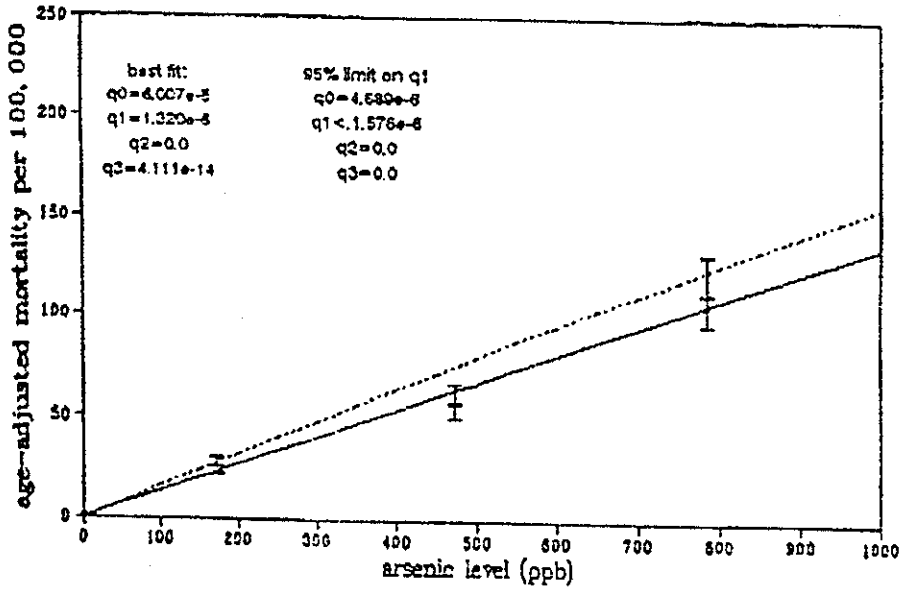

Fig. 7 Multistage model of female fatal bladder cancers as a function of arsenic dose rate in the study by Wu and co-workers [16]. —— best fit, ----- 95% limit on q1

Discussion

At least five hypotheses could explain different dose-response relationships for cancers of skin versus internal organs in the same cohort of persons exposed to arsenic. In summary, (a) nonarsenical substances associated with exposure to arsenic, or various metabolites of arsenic, might function as proximal carcinogens for different organ sites. (b) Some level of exposure might saturate a limited human capacity to metabolize arsenic, so measures of dose rate poorly reflect the dose of arsenic delivered to tissues. (c) Arsenic might accelerate a later stage of the carcinogenic process in skin than in internal organs. (d) Measures of dose rate might reflect tissue insult differently in different tumors because of nonlinearities in the biological mechanism that relates delivered dose of arsenic to the expression of cancer. (e) Irregularities might exist in the Taiwanese data.

Different proximal carcinogens for different organs

F.J. Lu has pointed out that the well water consumed by the Taiwanese cohort contained many substances besides arsenic, and some of them correlate with arsenic concentration [25]. The water supply in Inner Mongolia has similar characteristics yet there are differences in health outcomes. For example, no blackfoot disease is seen in Mongolia although other symptoms of chronic arsenicism are found [10]. High levels of organic materials, including humic acids occurred in the Taiwanese well water. In the presence of arsenic, or other transition metals capable of readily changing valence, which serve as catalysts, humic acids undergo a well-described reaction and generate fluorescent and/or highly mutagenic substances. Thus, arsenic levels will correlate with the levels of the mutagenic humic acid byproducts.

Lu [25] initially investigated the possibility that these humic acid byproducts caused Blackfoot disease. How-

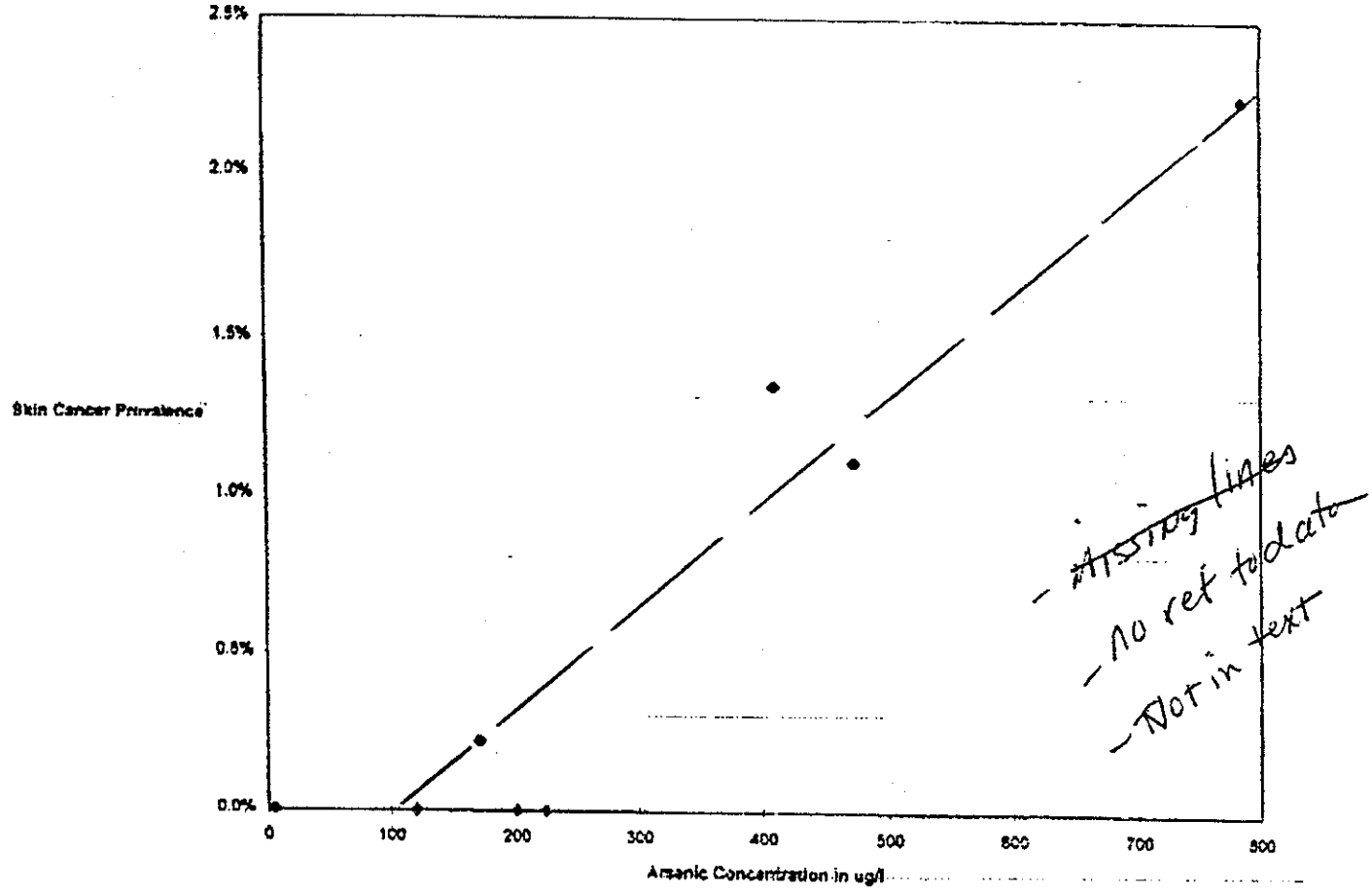

Fig. 8 Skin cancer prevalence rate by arsenic concentration in drinking water – all literature. —— best fit, ----- 95% limit on q_1

ever, his preliminary results suggest that the humic acid byproducts are potent bladder carcinogens. If inorganic arsenic only induces human skin and lung cancers, then it becomes easier to understand why bladder cancer apparently occurs only after ingestion of drinking water, since inhalation studies involve arsenic exposures in the absence of humic acids.

Apparently, no epidemiology studies of arsenic in drinking water have systematically characterized the presence of humic acids or humic acid byproducts, or examined whether these substances account for the association with bladder cancer (or other cancers) more strongly than arsenic. Further, we see no reason to limit the search for confounding exposures to humic acid byproducts. For example, selenium and fluoride levels generally correlate with arsenic levels in groundwater, and these substances can modify the effects of arsenic [26]. The presence of other carcinogenic substances, or modifiers of carcinogenesis, at levels that correlate with arsenic in drinking water, might provide satisfactory explanations for the interspecies and interorgan inconsistencies in arsenic carcinogenesis. In theory, substances in drinking water could suppress the lung cancer response observed after arsenic inhalation, while other substances could induce cancers of skin and internal organs.

Saturation of metabolism

Humans are directly exposed to arsenite (As+3), the reduced form of inorganic arsenic, as well as arsenate (As+5), the oxidized form, depending on the oxidation/reduction state of their water supply, whereas most bioassays tested only arsenate. Species differences might reflect differential exposure to arsenite. Indeed, the U.S. National Toxicology Program has a bioassay of arsenite in progress.

Arsenate is less acutely toxic than arsenite. Arsenate absorbs better than arsenite, possibly because arsenate reacts less with gastro-intestinal tract membranes [27]. In biological systems, however, arsenate and arsenite interconvert freely, depending on the oxidation-reduction state in the gastrointestinal tract and body. Higher arsenic levels in drinking water will directly alter the reducing capacity of the water. Mammals also excrete arsenic into bile with greater appearance after arsenite than arsenate administration. In either case, the gastrointestinal tract rapidly and efficiently reabsorbs arsenic from bile [28].

At a whole body level, the distribution of absorbed arsenate depends on clearance from blood. Man, dog, mouse, and rabbit clear absorbed arsenate rapidly, with 90% of the administered arsenic disappearing with a half-life of one to two hours, followed by a second phase of clearance with a half-life of approximately thirty hours and a third phase clearance with a half-life of approximately two hundred hours [28]. In contrast, rats accumulate arsenic in

blood, through binding to red blood cells, and exhibit a half-life of sixty to ninety days [28]. Absorbed arsenite reacts directly with thiol groups in plasma. Humans at autopsy, or rabbits and mice exposed to arsenite or arsenate, have elevated levels of arsenic in liver, kidney, lung, and intestinal mucosa [29].

In mice, uneliminated arsenic accumulates in bone, kidney cortex, intestinal mucosa, and hair follicles [30]. Arsenate is isosteric and isoelecronic with phosphate, resulting in arsenate substitution for phosphate. One consequence of this exchange is the distribution of arsenic into bone matrix, specifically into apatite crystals [31]. Furthermore, arsenate can function as a substrate for many enzymes in place of phosphate [32].

When dose rate is modeled, dietary intake may not influence parameters, because drinking water levels may generally correlate with dietary levels. Often, drinking water also supplies local agriculture, resulting in a feedback loop. Thus, drinking water dose rate could serve as an indicator of overall arsenic exposure but still not constitute the major source of arsenic. Clearly, exposure through drinking water ingestion can have dramatic effects on the risk of skin cancer, although only approximately one-third of total arsenic intake usually arises from drinking water.

At a cellular level, arsenate rapidly accumulates within cells, via a phosphate pump [33]. All animals rapidly reduce intracellular arsenate to arsenite; glutathione appears responsible for almost all such reduction [34]. Intracellular inorganic arsenic either enters the phosphate pool as arsenate or conjugates with glutathione as arsenite. Approximately one-third of absorbed arsenic binds to thiol groups of structural proteins in the form of arsenite, and reducing agents, such as mercaptoethanol, can release it into solution [35]. The overall effect is to trap arsenic within cells in the vicinity of the site of absorption, but the specificity of uptake is influenced by tissues rich in thiol groups, i.e., keratin-rich tissues, such as skin, hair, or cuticle.

The major metabolites of inorganic arsenic are monomethyl arsenate (MMA) and dimethyl arsenate (DMA; cacodylic acid). The biochemistry of arsenic methylation is poorly understood, but it appears to involve a glutathione-arsenite complex as substrate [35]. All three arsenic species (inorganic, MMA, and DMA) are excreted in urine by humans. Most evidence supports the hypothesis that the process of arsenic methylation is primarily a detoxifying process [4], however there is evidence that DMA may be a proximal toxicant for some endpoints [34].

DMA apparently induces tetraploidy in cell cultures [36]. DMA also enhances kidney carcinogenesis [37] and bladder carcinogenesis [38] in animal bioassays. Yamanaka and coworkers [39] speculate that tumor promotion by DMA may result from DNA strand scission by oxygen radicals arising from the reaction of DMA with molecular oxygen.

The extent of methylation in intact animals depends on the valence of the arsenic administered. Arsenite yields a greater degree of methylation in rats and mice than arsenate [28]. Since arsenite appeared before DMA in the urine of rabbits given intravenous arsenate, arsenate must be reduced to arsenite prior to methylation [40]. Methylation also depends on the species [28, 29]. Marmoset monkeys are the only species so far identified that show virtually no methylation of inorganic arsenic. Mice and rabbits also methylate inorganic arsenic. In both species almost all arsenic is excreted as DMA.

While it is easy to understand how different arsenic metabolites could serve as proximal carcinogens at different organ sites, and while it is easy to understand that differential localization of arsenic after different routes of exposure could lead to different patterns of cancer induction, it remains difficult to explain the absence of evidence that skin, bladder, or kidney cancers occur after arsenic inhalation, solely on the basis of metabolism. Ingested arsenic will undergo first pass metabolism through the liver before entering the general circulation, whereas approximately one-third of the arsenic absorbed after inhalation passes through the liver, but this difference can not account for the inconsistencies in organ-site pattern between inhalation versus ingestion epidemiology studies.

The hypothesis has been advanced that humans have limited metabolic capacity for arsenic methylation and, thus, that the nonlinearity in the dose-response relationship for skin cancer reflects saturation of detoxification [41]. The idea is that human liver methylates most arsenic below some dose rate, and, when methylation capacity is saturated, inorganic arsenic is delivered to other tissues. The misconception that saturation of detoxification would lead to a threshold, below which arsenic would not induce cancer, probably has generated more attention for this hypothesis than it deserves. Saturation of detoxification actually implies a shift in potency at lower doses, but not a threshold.

The data analyzed in this paper suggest that kidney and bladder cancers apparently have linear dose-response relationships, but skin cancer prevalence is a highly nonlinear function of arsenic dose rate. It is difficult to understand how arsenic metabolism could saturate among some members of a cohort who develop skin cancer, but not saturate for persons in same cohort, who develop internal organ cancers. No good evidence exists that only methylated forms of arsenic circulate in humans, but this is a testable hypothesis. In addition, the hypothesis of saturable human methylation capacity is at variance with the idea that arsenic metabolism occurs on a more regional basis, depending on route of administration, for example.

Oral administration of arsenate to humans, mice, and dogs resulted in humans eliminating 68% of the dose in one week and mice and dogs eliminating 99% of the dose in a week [28]. Humans are the only species to excrete MMA in addition to DMA [29], and this evidence is cited in support of saturable human methylation capacity. There is, however, no good evidence that the urinary excretion of inorganic arsenic, MMA, or DMA reflects metabolic capacity instead of renal handling.

If high arsenic levels do saturate human methylation capacity, not renal handling of metabolites, methylation of DMA should plateau at higher arsenic exposures, and the

ratio of MMA to DMA should dramatically increase. No good quality evidence demonstrates such an excretion pattern. Excretion patterns of arsenic metabolites also are difficult to interpret, because methylation capacity reflects dietary status. A high dietary arsenic load could deplete metabolic reserves of glutathione, shifting the arsenate to arsenite level, and diminishing the precursor for methylation. Thus, higher arsenic exposures might well lead to higher arsenite exposures.

Valentine and coworkers [42] measured total arsenic levels in human blood, urine, and hair in five different communities, each with different and variable arsenic levels in drinking water. They found increases of arsenic in urine and hair with increasing drinking water concentrations over a range from 6 to 393 ppb, but no increase in blood concentration until drinking water levels reached approximately 100 ppb. The correlations were established using group averages, instead of data for each individual in the cohort. No correction was made for the contribution of arsenic from food. Individual arsenic metabolites were not measured. In contrast, Smith and coworkers [6] did measure levels of individual arsenic metabolites in the urine of workers exposed after inhalation of arsenic trioxide. They found no plateau in DMA excretion with increasing urinary output, and no notable change in MMA to DMA ratio occurred.

If rodents had much greater methylation capacities than humans, higher arsenic levels in bioassays would not saturate animal metabolism, and detoxification could explain the inconsistency in species specificity of arsenic as a carcinogen. Unfortunately for this hypothesis, rats excrete only 4% of the administered inorganic arsenic as methylated forms of arsenic [28], yet rats do not develop tumors in response to arsenic exposure. Several labs are developing physiological pharmacokinetic models to describe the absorption, distribution, metabolism and excretion of arsenate, arsenite, MMA, and DMA. Because some arsenic metabolites bind covalently to structural macromolecules and/or undergo intracellular sequestration, construction of adequate deposition models for each human organ likely will prove difficult. Eventually, better quality data and good models may resolve the questions about the role of arsenic disposition in carcinogenesis.

Overall, neither hypotheses that invoke saturation of human methylation capacity nor inconsistencies in the Taiwanese data explain the inconsistencies in the induction of cancer by arsenic. The disposition of arsenic inevitably plays a role in the induction of cancer and merits more study, especially the idea of regional metabolism and distribution. It is worth recalling that most inhaled arsenic is in particulate form, which may help explain some of the inconsistencies of effects after different routes of exposure.

Late stage carcinogenesis

Application of the multistage model to lung cancer data from a cohort of copper smelter workers suggested that arsenic acted on a late stage [43]. The analyses of skin, but not bladder or kidney, cancer data in this paper are consistent with this hypothesis, because late stage carcinogens exhibit highly nonlinear dose-response relationships. Thus, arsenic might accelerate a late stage of the carcinogenic process in skin but an early stage in kidney or bladder. If the late stage is irrelevant to the carcinogenic process in rodents, or if rodents lack initiated cells, late stage carcinogenesis also might explain the species specificity of arsenic carcinogenesis. Late stage carcinogenesis does not, however, explain the exposure dependent pattern of organ sites in humans.

Nonlinear dependence of mechanism on delivered dose

Measures of dose rate may poorly reflect carcinogenic potency, because arsenic acts on some enzymatic or receptor-mediated process which has a nonlinear dose-response relationship. The leading candidate for such a process is stimulation of cell proliferation. Arsenic is not mutagenic in the traditional sense of either generating DNA adducts or inducing revertants at specific loci [44]. Arsenic does induce both cell proliferation and clastogenic events in Syrian hamster embryo cells [45]. Arsenic does not, however, appear to induce cancer in Syrian hamsters.

The mechanism of arsenic-induced cell proliferation is not yet known. Following exposure of intact rodents or cells in culture to arsenic, induction of heat shock proteins and metallothionine occurs [46]. These effects precede more obvious manifestations of chronic cell injury. It may be that arsenic modifies the release of some factor that controls cell proliferation or changes the activity of this factor once bound to cells.

Cell proliferation alone can provide a sufficient explanation of carcinogenesis [47]. Such a mechanism has important consequences for the dose-response relationship. If arsenic promotes the transformation of previously initiated cells through the induction of cell proliferation, a nonlinear dose-response relationship will result, similar to that observed in Fig. 1. If cell proliferation alone induces cancer, by increasing the number of cells at risk of spontaneous mutation, a true threshold should occur, but any mechanism involving a simultaneous increase in the initial mutation rate by arsenic will not generate a threshold.

Aberrant cell proliferation can lead to abnormal mitosis, resulting in chromosomal abnormalities. Clastogenesis alone can induce cancer. The likely mechanism is the loss of suppressor genes after inactivation during chromosomal rearrangement. Thus, hypotheses about arsenic-induced cancer that depend on late stage carcinogenesis or cell proliferation are not exclusive of each other.

Keratoses, a definitive sign of aberrant cell proliferation, were noted at earlier times and in a higher proportion of the arsenic exposed persons in the Taiwanese cohort [12]. Further, skin cancer incidence did not occur independently of the incidence of keratoses. Like skin cancer, the prevalence of keratoses also correlated with age. Persons with keratotic lesions were at much greater risk of

skin cancer. The keratoses in the cohort were neither quantitatively attributed to specific individuals, who either did or did not get skin cancer, nor were shown to precede skin cancers at the same anatomical sites, so a precursor-successor relationship was not established. Clastogenic effects also have been noted in humans exposed to arsenic [48]. A mechanism of arsenic-induced human cancer that involves cell proliferation would explain both species specificity and different dose-response relationships for different organ sites, but it is difficult to see why different routes of exposure would generate different patterns of cancer, based on this mechanism.

Data irregularities

Some anomalies have surfaced in the Chen data [49, 50]. Wide variations in arsenic levels occurred at several villages and excessively high mortality rates attributed to arsenic were observed in some villages with only low arsenic levels in the drinking water. Thus, some distortion of the dose-response relationship is likely, and this misclassification probably applies to the Tseng study of skin cancer as well, since it used the same exposure data. Because the arsenic levels in the water supply varied across wells in the same village and temporally in the same well, even individual exposure specifications represent averages. The death certificate data for the Chen cohort appear sound, but similar reservations apply to them as for all retrospective studies based on death certificates. For this reason, it seems unwise to place much confidence in the exact parameters of any model fit to similar epidemiology data.

The effect of exposure reclassification would be to move some individuals from one exposure category to another. If this occurred at random, our conclusion, that the dose-response relationship for skin cancer differed from the dose-response relationships for internal organ cancers, would not change. Only if, for example, deaths related to skin cancer in the highest exposure category were selectively misclassified from the lowest exposure category, would the relative differences, and our conclusions, change. This seems unlikely. The Taiwanese drinking water supply was remediated in the mid-1950's, and it may now be impossible to establish precise quantitative exposures. While we have no problem with efforts to evaluate the adequacy of the data (or to refine them) retrospectively, for purposes of risk assessment, our response to recent criticism of the Chen and Tseng studies is that they neither undertook nor published a risk assessment. Scientifically, their work appears sound, because independent studies have replicated their main conclusions: prevalence correlates with dose rate and with duration of exposure. The exposure data appear, however, too imprecise for reliable risk estimation.

We are continuing our evaluation of dose-response relationships for internal cancers in the Taiwanese cohort, but the exposure data appear, however, too imprecise for reliable risk estimation.

We are continuing our evaluation of dose-response relationships for internal cancers in the Taiwanese cohort, thus little biological sampling is possible. In addition, independent replication of the studies with an unrelated cohort is always desirable. For these reasons, we hope to study a new population in Inner Mongolia [10].

Arsenic-associated cancer remains a significant worldwide public health problem. There are reasons to believe that arsenic still contributes significantly to overall U.S. cancer risk, despite the high quality of U.S. drinking water. This belief has two different bases. One is that arsenic-induced skin cancer is biologically different and more lethal than sunlight-induced skin cancer, but the cases of arsenic-induced skin cancer get lost in the much higher prevalence of sunlight-induced skin cancer. The other belief is that arsenic may account for a substantial portion of all U.S. bladder cancer. Based on extrapolation of data from ingestion studies and a U.S. case control study, Alan Smith and coworkers [51] have suggested that the low levels of arsenic present in U.S. drinking water might cause a major portion of the bladder cancer cases.

Acknowledgement We thank Barbara Beck, Kenneth Brown, D. Warner North, and Randy N. Rob for their comments on an earlier version of this manuscript.

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Arsenic and Bladder Cancer: The US Experience- A US study based on 75 million person years of observation (1950-1979)

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BACKGROUND: Prior to 2002, the US drinking water standard for arsenic was 50 ug/l. Based on data from Southwest Taiwan with arsenic drinking water levels of 400 (+) ppb, NRC and EPA predicted a significant increased risk at 50 ug/l arsenic with a lower risk at 10 ug/l arsenic. The NRC predicted a bladder cancer death per ug/l arsenic risk of + 4.6 E-05 at and below 50 ug/l.

STUDY DESIGN: Data from three governmental sources produced a US dataset on thirty-year (1950-1979) bladder cancer mortality (National Cancer Institute) in 133 US counties known to depend on ground water as their drinking water source (per state departments of the environment) and with ground water median arsenic concentrations of 3 ug/l or greater (United States Geological Survey), which were analyzed for a dose-response relationship.

RESULTS: The median drinking water arsenic concentration in these 133 counties ranged from 3 to 59 ug/l (ppb), and the 1960 census showed a white male population of 2.5 million. A 30-year mortality observation period (1950-1979) yielded a study of 75 million person-years of observation. Over all, the lifetime risk of bladder cancer mortality for white males was 0.005 (1/200), and no increase was observed with increased level of arsenic in the drinking water (3-59 ppb). Linear regression showed a negative slope indistinguishable from zero, revealing no evidence of an arsenic-dependent risk in this exposure range. The slope (lifetime increased risk per 1 ug/l arsenic exposure) is –4 E-06 with 95 % confidence limits of –5 E-05 to +4.2 E-05 with an R-squared of 0.0002.

CONCLUSION: The WM bladder cancer mortality rate in the US is seen to be independent of drinking water arsenic concentration in the range of 3-59 ug/l (ppb). The NRC predicted risk of + 4.6 E-05 for bladder cancer mortality based on Taiwanese data is inconsistent with US experience.

Abstract for Presentation at the United States Geological Survey Conference (USGS), Natural Science and Public Health: Prescription for a Better Environment, April 1-3, 2003

Arsenic Does Not Appear to be the Risk Factor for Bladder Cancer in the Absence of both Humic Acid and High Arsenic Levels (> 350 ug/l)

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BACKGROUND: Since the 1980s, the US risk analyses for arsenic in drinking water have been based on observations from the Blackfoot-Disease endemic area of SW Taiwan where the artesian wells contained humic acids and high arsenic levels (350-2,000 ug/l) and the shallow wells lacked humic acid and had low arsenic levels (0-300 ug/l). Some villages had wells from both sources. Early studies analyzed risk by well source; Later studies analyzed only by mean arsenic level for wells in each village. Both water factors have not been analyzed together.

STUDY DESIGN: We have examined the data underlying the NRC 2000 analysis in order to examine the bladder cancer risks according to water source and then to identify the additional information that was learned from examining the specific arsenic levels within the water source groups.

RESULTS: We found that the bladder cancer mortality risk was not associated with the arsenic level in villages that used either only shallow wells as their drinking water source (10-300 ug/l) or both shallow and artesian wells as their drinking water source (ug/l). We found that only for the artesian wells did the bladder cancer mortality increase with increasing level of arsenic.

CONCLUSION: We find no arsenic-related bladder cancer risk with the exception of villages solely dependent upon humic acid-containing water with high arsenic levels above 350ug/l.

Abstract for Presentation at the United States Geological Survey (USGS) Conference, Natural Science and Public Health: Prescription for a Better Environment, April 1-3, 2003

A Re-Examination of SW Taiwan Bladder Cancer Mortality Studies

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OBJECTIVE:

To examine the consequences of disaggregating two exposure metrics in studying the relationship between well water arsenic level and bladder cancer mortality risk in SW Taiwan.

SUMMARY:

- Arsenic in drinking water and cancer risk assessments are usually based on data from the Blackfoot Disease (BFD) endemic areas of SW Taiwan.
- Data used in the bladder cancer risk assessment reveal an unexplained discontinuity in the dose-response curve at about 400 ug/l (ppb).
- Analyses of cancer rates in this area before 1990 distinguished artesian well water supplies from non-artesian supplies. Morales et al. (2000) did not include this distinction.
- Including this distinction in a reanalysis of the data indicates a separate artesian well dependency risk factor, possibly humic acid.

BACKGROUND:

- Morales et al. analysis is the basis for carcinogenic risk assessments for arsenic in US drinking water conducted by the National Research Council (NRC 1999; NRC 2001) and USEPA (2001).
- Analysis of bladder cancer mortality risks reported by Morales et al. reveals an unexplained discontinuity in the dose-response relationship at about 400 ug/L (ppb) (Figure 1).

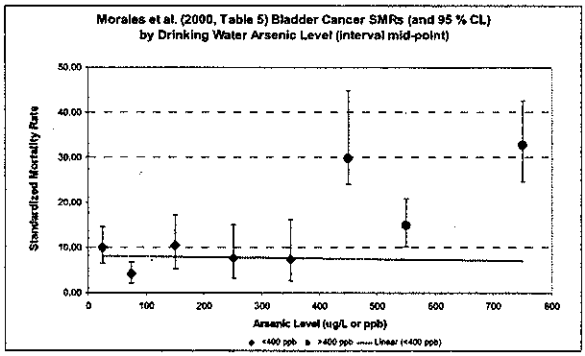

Figure 1

- The analysis presented in Morales et al., however, does not reflect this discontinuity. Under the assumption that the only relevant measure of exposure is arsenic concentration, regression analysis conforms to a linear dose-response relationship (Figure 2) that obscures the difference revealed in Figure 1.

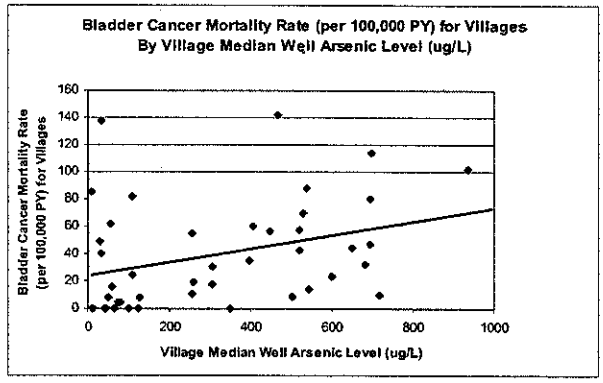

Figure 2

RE-EXAMINATION:

- CJ Chen et al. (1985) showed bladder cancer mortality rate depended on well type: artesian, shallow, or mixed (shallow and artesian) (Figure 3).

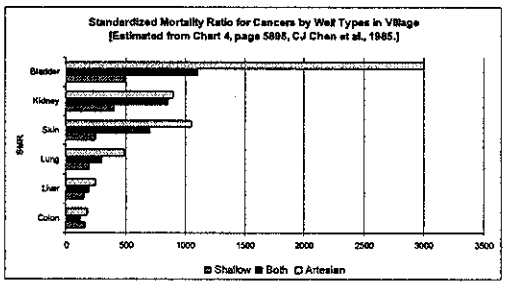

Figure 3

- This suggested that the type of well (artesian v. non-artesian) may influence the dose-response relationship between arsenic concentration in drinking water and bladder cancer mortality rates, and reanalyzing SW Taiwan data in terms of the artesian/non-artesian distinction can explain the discontinuity in the dose-response relationship observed in Figure 2.

- Figure 4 plots separate dose-response curves for villages solely dependent on artesian well (in **bold**) and other villages.

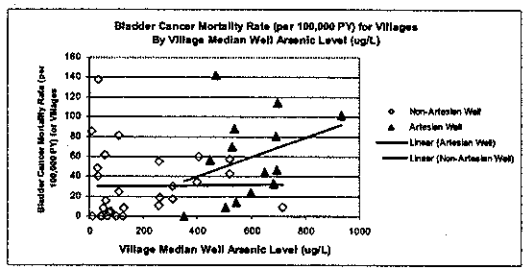

Figure 4

- The two-level stratification reveals the same discontinuity in Figure 1 and indicates that arsenic level is not the sole determinant of bladder cancer mortality risk in these villages.
- Dose-response relationship appears only in artesian well dependent villages with arsenic levels above 400 ppb. No such relationship for other villages with median water exposures of 10 - 750 ug/L arsenic is apparent.

DISCUSSION:

- Although the identity of the artesian well related risk factor is not known, its presence should be acknowledged in analyses.
- Humic substances present in the artesian well tanks that affect blood coagulation and are associated with conditions similar to BFD may be one such risk factor (FJ Lu et al.1975, 1990).
- Tully et al. (2000) suggest a mechanism by which humic acid at 50-100 uM yields gene expression in the presence of 50–100 uM arsenic.
- Whether such high arsenic levels are necessary in the urine to induce bladder cancers is not known.

EVALUATION OF RISK TO CHILDREN USING ARSENIC-TREATED PLAYGROUND EQUIPMENT

A REPORT PREPARED BY

CONSULTANTS IN EPIDEMIOLOGY
AND OCCUPATIONAL HEALTH, INC.

FOR SUBMISSION TO THE

CALIFORNIA STATE
DEPARTMENT OF HEALTH SERVICES

JANUARY 15, 1984

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EVALUATION OF RISK TO CHILDREN USING ARSENIC TREATED PLAYGROUND EQUIPMENT

I. INTRODUCTION

Arsenic treated playground equipment has been shown to be a potential source of Arsenic (V) exposure for children. The recent studies performed by the California State Department of Health Services (Cal/DOHS) confirm: 1) arsenic can transfer from the surface of playground equipment to the hands of persons (including children) who use arsenic treated wooden playground equipment; and 2) that it can be washed off the hands. These studies have raised a number of important questions including: 1) how much Arsenic (V) might be transferred to children who play on the equipment; 2) how much Arsenic (V) might children then ingest through licking their hand or transferring the arsenic to their food; and 3) how might this amount of Arsenic (V) exposure compare with other potential and permitted Arsenic (V) exposures. While there is never enough information to answer precisely each question that can be asked, there are sufficient data available upon which to base answers to these questions.

Further, the concern has been raised that the ingestion by children of arsenic (V) from playground equipment might increase their risk of skin cancer. Risk estimates have been made of the maximum potential risk of skin cancer from arsenic

exposure. These potential risks can be compared with other skin cancer risks to which children are exposed. The presumption that Arsenic (V) ingestion carries a carcinogenic risk is based on numerous assumptions from the scientific and medical literature that must therefore be assessed. Finally, the testing method used to measure potential exposure should be evaluated to assure that it produces valid reproducible results.

The evaluation of the skin cancer risk for children from Arsenic (V) in treated wooden playground equipment should be based on an assessment of the comparative magnitude of the exposure, the comparative risks of skin cancer and the strength of the association between Arsenic (V) exposure and skin cancer. Each of these topics will be considered.

II. ENVIRONMENTAL EXPOSURE ESTIMATES

Arsenic (V) is a ubiquitous element in the earth's crust with which people have daily exposure, whether or not they use arsenic treated playground equipment. The arsenic in the soil is Arsenic (V), as is generally the arsenic in water. When solubilized in either water or in 1 N HCl (one normal hydrochloric acid), Arsenic (V) from water, from soil, or from arsenic treated wood cannot be easily differentiated from each other.

The accompanying calculations attempt to estimate the size of each of these environmental exposures to Arsenic (V).

TABLE I

TABLE 3-6. A COMPARISON OF ARSENIC LEVELS IN ARSENIC-TREATED AND UNCONTAMINATED SOILS IN NORTH AMERICA

Sampling site	Total As content, ppm		Crop
	uncontaminated soil	treated soil[a]	
Colorado	1.3 - 2.3	13 - 69	Orchard
Florida	8	18 - 28	Potato
Idaho	0 - 10	138-204	Orchard
Indiana	2 - 4	56 - 250	Orchard
Maine	9	10 - 40	Blueberry
Maryland	19 - 41	21 - 238	Orchard
New Jersey	10.0	92 - 270	Orchard
New York	3 - 12	90 - 625	Orchard
North Carolina	4	1 - 5	Tobacco
Nova Scotia	0 - 7.9	10 - 124	Orchard
Ontario	1.1 - 8.6	10 - 121	Orchard
Oregon	2.9 - 14.0	17 - 439	Orchard
	3 - 32	4 - 103	Orchard
Washington	6 - 13	106 - 830	Orchard
	8 - 80	106 - 2553	Orchard
	4 - 13	48	Orchard
Wisconsin	2.2	6 - 26	Potatoe

[a] These are results from soils that had been repeatedly treated with an As pesticide or defoliant. Soils treated experimentally are not included.

Source: Walsh and Keeny (1975).

1.0 Water

The California report has already calculated that levels of Arsenic (V) intake from drinking water would be up to about 3.5-4.0 ug/kg/day, assuming a concentration equal to the (US) Environmental Protection Agency (EPA) drinking water standard (50 ug/m/l).

2.0 Soil

2.1 Concentration

There are no standards for acceptable soil levels of arsenic. However, available data that demonstrate a range of arsenic levels in normal soils and a range of levels in contaminated soils can be used for estimating a normal soil aresenic level. In the 1983 draft review of EPA's Health Assessment of Inorganic Arsenic document, the EPA stated that "background levels of arsenic in soils range from less than 1 ppm to above 40 ppm", and that relative increases to this background level from industrial sources can be of the order of 100 times greater. Our table 1 (EPA's table 3-6 on page 3-20 in their document) presents arsenic levels for uncontaminated and contaminated soils.

2.1.1 "Typical" Estimate

The left hand column in Table 1 can be used to estimate typical levels of arsenic in ordinary dirt. These data show ordinary levels of arsenic in untreated ("virgin") soil to

range from zero to 80 ppm. The mid-range of these numbers, 40 ppm, might at first glance be taken as a typical value. However, as it lies within the range of only two of the seventeen data sets, we would judge that it would be too high a value to represent a "typical" level.

We have tried to develop a reasonable single statistical summary of the information in this column by first finding the mid-range value for each set and by then obtaining the average value of the mid-ranges. This average mid-range value is 10.4 ppm. If the highest and lowest mid-range values are eliminated from the average so that the result is not skewed by aberrant values, the average becomes 8.7 ppm. Thus, 9-10 ppm seems to be a reasonable "typical" value for generally accepted arsenic soil levels. For our calculations, we will use 9.5 ppm.

2.1.2 "Worst Case Estimate"

Based on the same data, we might use 80 ppm as the "worst case" concentration of acceptable arsenic levels in the soil, since that is the highest level reported by the EPA in uncontaminated soils. However, this value may be an aberrant value.

We might use 40 ppm as an acceptable high normal concentration for comparative analyses, based on the EPA's observation, however, it is probably a low estimate of the "worst case" as it is still in the mid-range for the normal soils.

Alternatively, we might choose the EPA hazardous waste

criterion as a basis for determining an upper limit of acceptable arsenic level in soil (or a lower limit of unacceptable arsenic in soil). That criterion would not consider soil as being a hazardous waste unless it contained 100 ppm arsenic extractable at pH 5. If we further assumed that 100% of the arsenic in soil was extractable at pH 5 (laboratory work indicates that about 5% is extractable at pH 5), then the upper bound or "worst case" estimate would be 100 ppm. Thus, we have three different values --40 ppm, 80 ppm and 100 ppm-- that might be chosen to represent the "worst case" estimate of acceptable soil arsenic concentration. 40 ppm appears to be too low an estimate. 80-100 ppm might be more appropriate as an estimate of the "worst case" normal level.

2.1.3 Treated vs. Uncontaminated Soils

Similar calculations based on the data given in Table 1 for the treated soils give an average mid-range value of about 200 ppm. With the upper and lower outliers removed, the average mid-range value is approximately 135 ppm. If 135 ppm is considered a "typical" concentration of treated soils, then, there is at least a ten-fold difference in arsenic concentrations between "virgin" soils and "treated" soils. The levels in many of these "treated" soils would have exceeded the EPA criterion for hazardous waste, if their arsenic content had been fully extractable at pH 5.

2.2 Exposure

Arsenic in the soil has little solubility in water but is fully extractable in 20% nitric acid. We might assume, therefore, that it is probably 100% extractable in 1 N HCl. Little absorption of the solubilized arsenic could be expected from ingestion for persons with achlorhydria; but for those with normal gut physiology, about 10-40% absorption may be expected, based on studies in dogs. Cal/DOHS used an upper estimate of 30%. We will use the same for ease of comparison.

Thus, one can estimate that about 100% of the total arsenic in the ingested soil could be extracted in passage through the stomach and that about 30% of the extracted arsenic could be absorbed in the gut. Therefore, 30% (100% x 30% = 30%) of an ingested soil dose may be expected to be absorbed.

Dosage. A calculation can now be made to estimate the normal amount of arsenic a child can be expected to absorb from ordinary ingestion of soil during play. For the purposes of our calculations, we have chosen a two and a half year old child, because this is an age group at which use of playground equipment begins and in which the greatest dirt exposure occurs.

Consider a "typical" exposure for an ambulatory two and a half year old child:

Daily Soil Ingestion = 10 grams

Arsenic Concentration = 9.5 ppm

Daily Arsenic Ingestion = 95 ug

Children's exposure to soil will be by inhalation, ingestion or dermal absorption. The Centers for Disease Control, Atlanta, Georgia (CDC) has recently assessed the magnitude of soil exposure of children, based on their studies of lead levels in children living near lead smelter environments.

2.2.1 Inhalation

It is assumed that soil particles are of greater than respirable size, and would, therefore, precipitate into the nasotracheal mucous blanket, with which they would be swallowed. Therefore, this exposure would be included in the assessment of ingested arsenic. Arsenic in soil has little aqueous solubility, so if respirable size particles stayed in the lung, there is little chance of easy dissolution.

2.2.2 Ingestion

Soil Amount. CDC developed the following table of childhood soil exposure patterns by age.

Table 2

Daily Soil Exposure Patterns by Age

Age Group	Soil Ingestion	Soil Adsorption
0-9 months	0 grams	0 grams
9-18 months	1 gram	1 gram
1.5-3.5 years	10 grams	10 grams
3.5-5.0 years	1 gram	1 gram
5.0+ years	0.1 gram	0.1 gram

Absorption Rate	=	30 %
Arsenic Gut Absorption	=	28.5 ug/day
Average Weight	=	12.6 kg
Arsenic Absorption Rate	=	**2.3 ug/kg/day**

An estimate of a higher normal and acceptable exposure for such a child based on 40 ppm arsenic in the soil would yield an estimated arsenic absorption rate of **9.5 ug/kg/day** (10 grams per day x 40 ppm x 30% / 12.6 kg = 9.5 ug/kg/day). An estimate of a higher exposure level of possibly borderline acceptibility for such a child based on 100 ppm arsenic in the soil would yield an estimated absorption exposure rate of **23.8 ug/kg/day** (10 grams per day x 100 ppm x 80% / 12.6 kg = 23.8 ug/kg/day).

2.2.3 Dermal Absorption

CDC has calculated that children adsorb to the skin as much dirt as they ingest. The comparative amount of arsenic absorption would depend on the comparative absorbability of arsenic from the skin and from the gut. We are aware of no studies on the dermal absorption rate of arsenic from soil. However, Peoples (1979) studied the dermal arsenic absorption from arsenic treated wood dust in dogs and found no evidence of dermal absorption. As the solubility characteristics of arsenic in sawdust and arsenic in soil are similar, we shall presume that there is, likewise, relatively little or no dermal absorption of arsenic from soil.

3.0 Playground Equipment

3.1 Cal/DOHS Exposure Calculations

The Cal/DOHS staff developed the following "worst case" assessment of arsenic exposure to children using arsenic treated playground equipment:

(A) Assume that child maximally transfers Arsenic (V) to his hands at the same surface density as maximally transferred to the "Kimwipe" in testing playground equipment (320 ug/100 cm^2);

(B) Assume active surface area of child's hands is 100 cm^2;

(C) Assume 30% absorption of ingested wooded Arsenic (V); and

(D) Assume that typical child weighs 20 kilograms.

Variations in these assumptions were made to develop a "typical" exposure estimate:

(A1) Surface density was assumed to be the same as the mid-range of the samples (162 ug/100 cm^2); and

(C1) Absorption was assumed to be 10%.

With these assumptions, the Cal/DOHS report calculated a "worst case" exposure per playtime of **4.8 ug/kg** and a more "typical" playtime exposure of **0.81 ug/kg.**

3.2 Comments on Cal/DOHS Exposure Calculations

If we assume one play period per day, the Cal/DOHS calculation shows a "typical" estimate of absorption rate (0.81 ug/kg/day) that is <u>less</u> than the "typical" daily exposure rate to natural ambient Arsenic (V) levels in dirt for a two and a half year old child (2.3 ug/kgday). The equivalent Cal/DOHS

maximum arsenic absorption rate prediction of 4.8 ug/kg/day is only twice this typical rate of 2.3 ug/kg/day; Further, it is only half the arsenic absorption rate of children living in other parts of the State or country where the soil level is 40 ppm., ie, up to about 10 ug/kg/day.

3.2.1 Worst Case Assumptions

The assumptions underlying the Cal/DOHS calculations need to be carefully considered. Assumptions (1) and (1A) are dependent upon a single unconfirmed laboratory test result of 320 ug/100 cm^2. The source of this value is unclear. It may be based on Cal/DOHS's report that the arsenic washed off the hands of a single volunteer who had vigorously rubbed playground equipment demonstrated a surface density similar to that of wood, up to 320 ug/100 cm^2. However, the data in that study seem to indicate that the 280 ug arsenic in the rinsate came from the full palmar surfaces of two adult male hands, which would have a combined palmar surface of about 300 cm^2. Thus, the hand testing appears to have revealed a surface density of only 90 ug/100 cm^2.

If the value came from the "Kimwipe" study, then it is 313.75 ug/100 cm^2 and, it is the <u>only</u> unreplicated measurement in a replicate sampling data collection schema. (Since no raw data is given, we are not sure with how many significant figures it is appropriate to report this data.)

A more appropriate value for the "worst case" estimate

would be 203.5 ug/100 cm^2, the highest mean of the replicates. This estimate could recognize that the same specimen was sampled by wiper A, whose samplings yielded a mean of 53.9 ug/100 cm^2. The mean of these two values is 128.7 ug/100 cm^2.

3.2.2 "Typical" Exposure

The Cal/DOHS "typical" exposure estimate is given as 162 ug/100 cm^2, the mid-range value of the individual measurements. Thus, it too is dependent upon the highest figure. Basing both the "worst case" estimate and the "typical" estimate on a single data point that itself may be in error is inappropriate. The "typical" exposure estimate should be based on values representing the central tendency of the data and not the dispersion of the data.

The average replicate mean can be used for a more "typical" exposure estimate. The average replicate mean for wiper Y is found to be 109.5 ug/100 cm^2; the average replicate mean for wiper A is 67.5 ug/100 cm^2. The arithmetic mean of these two values is 88.5 ug/100 cm^2. (The geometric mean is 86 ug/100 cm^2.)

Another approach might be to take the median replicate mean value, which would be 71.4 ug/100 cm^2. It is unclear which value is best, but the range of reasonable considerations appears to be about half that chosen in the Cal/DOHS calculations.

Assumption (2) that the active hand surface area exposed

daily from playground equipment to food or mouth by a child is 100 cm^2 needs verification. Just as the arsenic might transfer from the wood to the hands, it is also likely to transfer off of the hands and on to whatever object is next touched by the child. Activity studies would probably show that at almost all post-infant ages, the hands are more likely to go to the clothing, the body, the ground, or other objects, rather than to the mouth. The hands tend to go into the mouth only when they are sticky. Even during eating periods, the child's hands are quite likely to go first to the food wrapper rather than to the mouth; and further the child is then more likely to lick either the fingers or the palms, but not both sites.

4.0 Exposure Summary

The scenario analyzed by Cal/DOHS is an extreme situation that assumes "worst case" behavior continuously for the same child. Even under those circumstances, the maximal exposure still approximates the variability of normal exposures for children.

An indication that these exposures are within the normal range of variability is seen in the brief report in the October 1983 CUMTO-Tox Issue Review by the Cal/DOHS. In this report, an individual showed an elevation in his urine arsenic excretion rate after he ate fish, but not after he rubbed his hands on arsenic treated playground equipment and licked his hands. This is a very important observation that should be verified. These test conditions would involve adult hands (probably three

times larger than a child's) and a more vigorous licking than is assumed in casual contact with a child's food. As a result, the "delivered" dose was probably considerably greater than that of children who play on the wooden playground equipment.

The medical literature does not report skin cancer risk with arsenic exposure in the absence of signs of chronic arsenicism, nor does it report chronic arsenicism in groups that have not had increased urinary arsenic excretions. Further, the medical literature does not show evidence of adverse health effects from somewhat elevated arsenic exposures in children who show significant increases in their urine arsenic levels (Milham, 1977; Harrington, et. al. 1978; Morse, et.al, 1979; Southwick, et. al, 1982). If the children here show no increase in their urine arsenic levels, it is highly unlikely that there will be any adverse health effect ever found. Workers using the arsenic wood preservatives or working with products that use them showed no evidence of increased urinary arsenic levels and no evidence of adverse health effects (Gilbert et al., 1982).

III. Comparative Skin Cancer Risk Assessment

1.0 Risk Estimate from Playground Equipment

An August 10, 1983, document from the California State Department of Health Services entitled "Relevant Questions and Answers Related To Arsenic and Playground Equipment" indicates

that the individual lifetime risk for persons who use these playground equipments is "on the order of a few cases (of skin cancer) per hundred thousand" persons, if there is any excess risk. ("Few" has not been defined, but is generally accepted as meaning two to three, as seen in a 1984 telephone survey). For discussion purposes, we shall assume this lifetime risk may be 2.5 cases per 100,000 persons. This risk can be placed in the perspective of other risks of skin cancer.

2.0. Background Risk

The age-adjusted (1970,US) annual incidence rate of non-melanotic skin cancer in the Oakland area is 250 cases per 100,000 persons for men and 133/100,000 for women. Using the male data and assuming an average lifetime of 76 years (1976 US median), the lifetime skin cancer risk is calculated to be 19,000 per 10^5. (The Cal/DOHS document gave an estimate of a few cases per thousand, a value more appropriate for either melanotic skin cancer incidence or non-melanotic skin cancer mortality, but not non-melanotic skin cancer incidence).

3.0 Sun Related Skin Cancer Risk

The dominant factor in skin cancer epidemiology is the level of UV radiation. If we assume that UV radiation is the cause of all non-melanotic skin cancer in the area, we can estimate a dose-response ratio based on the level of exposure. The assumption may overestimate the association as it is unlikely that all non-melanotic skin cancers are due to ambient

sunlight. The methodology underestimates the association for it does not include a consideration of latency, but assumes that the carcinogenic dose extends past seventy five years. The methodology further markedly underestimates the association by assuming that the average resident is out-of-doors as much as a third of the potential sunlight time for his entire lifetime.

In 76 years, a resident would have 27,740 days of potential sun exposure. Let us further assume that a resident receives as much as one-third of the potential sun exposure. Calculation of the risk of skin cancer from UV radiation would predict a risk of **2 cases per 10^5 persons per day of sunlight** (19,000 cases/10^5 divided by 27,740 potential full days of sunlight x 1/3).

4.0 Comparative Risk

According to the 1975 NCI report on UV radiation and skin cancer, the average daily UV radiation in Oakland is 4129 units (based on 1974 data). Further calculation would predict a lifetime increased skin cancer risk of 2×10^{-5}/ 4129 UV units or 0.498×10^{-5}/ 1000 UV units. One can calculate the amount of sunlight exposure that might be equivalent to the Cal/DOHS estimate of the potential risk from playground equipment use, as follows:

$$\frac{2.5 \times 10\text{-}5}{0.498 \times 10\text{-}5/\text{UV}} = 5.024$$

Measurements of UV radiation per day varied in Oakland throughout the year from a low of 260 units in December to a high of over 9,000 units in June, and from an average of 997 units in December to an average of 7,537 units in June. 5,024 units is slightly less than the average daily exposure in April or September.

In summary, it appears that the lifetime risk of skin cancer, if any, from the use of arsenic treated playground equipment is probably less than the increased lifetime risk of skin cancer from staying out-of-doors on a single day in April.

It is not unreasonable to surmise that any increased lifetime risk of skin cancer for children using such equipment is as likely or more likely to come from the sunlight exposure than from the potential arsenic exposure from playground equipment.

IV. CARCINOGENICITY OF ARSENIC (V)

The assumption that Arsenic (V) is carcinogenic is based on the observations that Arsenic (III) has been shown to be a pulmonary carcinogen in the smelter environment and a dermal carcinogen from ingestion of arsenite medications (Fowler's solution), and that skin cancer has been reported to be in excess in areas with high arsenic content in the water, particularly in a study from Taiwan.

I.0 Drinking Water Studies

1.1 U.S. Studies

A number of studies have been conducted in the US to examine the relationship of arsenic levels in the drinking water to the frequency of skin cancer. (Morton, et. al, 1976; Harrington, et. al., 1978; and Morse, et. al, 1979) None of the U.S. studies has found an association, despite specific investigations. While individually each study may be considered to be too small or insensitive, as a group their negative finding is reassuring.

The more recent US studies have some marked improvements over earlier foreign studies. For instance, the CDC study by Harrington et al. is the only arsenic drinking water study to report the speciation of the arsenic. They report 20-40% of the arsenic to be Arsenic (III) and the remainder Arsenic (V). The arsenic concentrations were as high as 40,000 ug/liter with a mean of 224 ug/liter. No evidence of arsenicism or of excess skin cancer was found.

1.2 Taiwan studies

The Taiwan study reported a prevalence of skin cancer and of Blackfoot disease (Tseng, 1977) that were each similarly related to the consumption of arsenic-containing water. However, inadequate chemical analysis of the constituents of the water has been made. Therefore, it is difficult to assign a specific causal role to those few constituents who have been identified. The water has been shown to contain both arsenic and a fluorescent ergotamine-like substance. The diseases

found may be related to either constituent in the water or to some other as yet unknown constituent or to an interaction. It has been supposed that the Blackfoot disease is related to the ergotamine exposure and the skin cancer to the arsenic exposure, but this is only conjecture. Further, as the arsenic was not speciated into Arsenic (III) and Arsenic (V), it is not possible to attribute any effect specifically to either Arsenic (III) or Arsenic (V).

1.3 Chilean Studies

A second source referred to as indicating Arsenic (V) as an etiologic agent for skin cancer is the studies from Antofagasta, Chile (Zaldivar, et. al, 1981). In this case, Zaldivar in 1981 reports finding thirteen cases of skin cancer in residents of a neighboring province (Tarapaca, the northermost province of Chile). These cases were identified from the 1918-1946 hospital records of the University medical school hospital (a thousand miles further south in Santiago). All thirteen cases are in men working as miners in the saltpeter mines. They mined crude sodium nitrate containing about 2.5 ppm arsenic. He describes the young group of workers as having a "high prevalence of alcoholic cirrhosis (heavy intake of coarse wines) as well as a high prevalence of early and late syphillis (brothels near nitrate fields)". Zaldivar reports four recent well water arsenic specimen results from Tarapaca ranging from 0.24 to 2.0 ppm with a mean of 0.90 ppm and attributes the observed skin cancers to this well water

exposure. This study contains too many alternative arsenic exposures (occupational, local brew, etc.) and too many gaps (non-referral cases, cases in other industries, female cases, rates and comparative rates) for the attribution to be supported. Furthermore, there also has been no speciation to determine whether the exposure is to Arsenic (III) or to Arsenic (V).

2.0. Summary

The rest of the Arsenic (V) literature needs critical evaluation to determine if there is any evidence demonstrating an excess of any cancers among persons with Arsenic (V) exposures approximating in magnitude the exposure of persons playing on playground equipment. The studies of workers producing or using arsenic treated wood do not support such an hypothesis.

V. OTHER TOXICOLOGIC CONSIDERATIONS

In this discussion, we have given no specific attention to any risk of acute toxicity from Arsenic (V) exposure, because under these exposure conditions there is none. Further, we have not dealt with the carcinogenic risk demonstrations for Arsenic (III) as seen in the various smelter studies. Elsewhere, we have given a detailed analysis of the Arsenic (III) data which has lead us to conclude that Arsenic (III) may have a carcinogenic threshold, possibly at about 350-500 ug/m^3 in the occupational setting for a daily airborne exposure of 3.5 to 5 mg. The exposures under consideration here are not

airborne, they are not Arsenic (III), and they are far, far lower than the suggested threshold level. Thus, since it is fairly clear from the literature that there is extremely little, if any, in-vivo interconversion of Arsenic (V) to Arsenic (III), questions of Arsenic (III) carcinogenic risk are not central to the Cal/DOHS data. Finally, we have only briefly discussed the carcinogenesis literature or Arsenic (V), both because it has been so regularly criticized and because the exposure levels here apparently do not exceed normal levels.

VI. TESTING PROBLEMS

There are some difficulties in using the comparative arsenic wipe samples as a data base. Wiper A generally found 40% more arsenic on the replicate than on the original test wipe. Wiper Y had more reproducible sampling than did wiper A, but wiper Y had arsenic levels 2-3 times as high as those of wiper A. Small effects were also seen with copper and chromium testing. The intra- and inter-observer differences in the taking of wipe-samples can lead to markedly different assessments of the levels of arsenic. The attached appendix provides a more detailed statistical analysis of the data. However, it is clear that the testing process itself must be better standardized if it is to be part of a proposed exposure control system.

VII. SUMMARY

We find:

1) It appears that the maximal Arsenic (V) exposure estimate for children from use of playground equipment is within the normal variation of Arsenic (V) exposure for children;

2) The maximum estimate of the skin cancer risk associated with such exposure approximates the skin cancer risk from the sunlight experienced during play periods;

3) The scientific studies upon which the association of Arsenic (V) and skin cancer is based are weak; and

4) Finally, the sampling methodology used to measure the potential exposure from wood products is uncertain with little reproducibility by individual samplers or between investigators.

Report prepared
January 15, 1983 by

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ANALYSIS OF ARSENIC WIPE SAMPLES

Summary of Results

1. On average, person A's samples had a total arsenic level of 64.79 (ug per 100 cm^2), compared to an average level of 143.54 for person Y.

2. A sign test of the significance of the difference between the two means (64.79 vs 143.54) yields p = .031 (two - sided), in agreement with the paired t-test on ln (As) - p = .034 (two-sided).

3. The replicate measurements made by person Y were somewhat more consistent than those by Person A. The standard deviations of measurement error were σ_e = 12.03 (Person Y) and σ_e = 17.67 (Person A). [Note values of d_i in the table on p.3]

4. The measurements on the test areas made by Person Y indicated considerably more variability across areas than the measurements made by Person A. The estimated standard deviation of As across test areas was σ_t = 100.36, for Person Y compared to σ_t = 21.56 for Person A.

5. The logarithmic transformation of the data is beneficial insofar as it diminishes the effects of extreme observations. This can be seen by examining σ_e, σ_t, and sd (y_i) in relation to mean (y_i) on p.7, and comparing the results to those on p.4.

6. In summary, intra-and inter-observer differences in taking wipe-samples led to markedly different assessments of the level of As. A protocol for better standardizing the measurement process would appear to be worth developing.

General Comments:

1. The approach to the analysis of the wipe sampling data should be done in terms of a repeated measures (Winer 1971) design. Two persons, designated A and Y each took replicate samples on each of 6 test areas. [Area 7, noted "wood worn", has been excluded from the present analysis.]

2. Because of the repeated measures design, one should not approach the analysis as if the measurements were all independent, as was done in the analysis reported in the July 27, 1983 memorandum of Cal/DOHS.

3. Because of the "missing data" for Y2 on test area 2, one cannot use the standard repeated measures analysis that assumes no missing observations, unless one drops all of the measurements on test area 2, or unless one "imputes" a value for the missing observation. The summary of results is based on an analysis constructed from first principles, one that takes into account the repeated measures design and that does not discard or impute any observations (See pages 9-10 for an alternative analysis that discards a single aberrant observation).

4. The data are markedly non-normal when expressed in the original units of measurements (ug per 100 cm^2). As suggested in the July 27, 1983 memorandum, a log transformation improves the distribution of the data, insofar as normality is concerned.

5. In view of item 4 above, analyses are reported for both As and ln (As). The summary of results (p. 1) is given in terms of As for simplicity of exposition, but is applicable to both analyses.

6. The analysis presented bears a resemblance to an "unweighted analysis of cell means" (Snedecor and Cochran, 1980). The observation $X_1 = 313.75$ based on a single observation by Person Y on test area 2 (see p.3) is treated like the remainder of the X_1's, each of which is the mean of two observations.

References:

Winer B.J. (1971): Statistical Principles in Experimental Design, 2nd ed. McGraw-Hill, NY.

Snedecor G.W. and Cochran W.G. (1980): Statistical Methods, 7th ed. Iowa State University Press, Ames, pp. 414-421.

I. ANALYSIS OF ARSENIC

As Wipe Sampling: Total As (ug per 100 cm2) Data*

		Test Area 1	2	3	4	5	6
Person							
A	X_i	53.90	105.77	33.50	68.38	76.12	51.09
	d_i	42.80	28.70	5.12	-22.64	32.43	9.70
Y	X_i	203.75	313.75	76.09	71.42	144.25	52.00
	d_i	21.87	---	7.73	-24.36	-3.74	4.24

X_i = average As level for ith test area; $(x_2 + x_1)/2$

d_i = difference between replicate As measurements $(x_2 - x_1)$ for ith test area

note: X_i and d_i are reported separately for Persons A and Y

*This table is derived directly from the table entitled "Comparison of Wipe Sampling - Summary of Results"

As Wipe Samples: Analytic Summary*

	Person A	Person Y
mean (X_i)	64.79	143.54
sd (X_i)	24.92	100.72
n	6	6
mean (d_i)	15.35	1.15
sd (d_i)	24.99	17.01
n	6	5

	Person A	Person Y
σ_t**	21.56	100.36
σ_e***	17.67	12.03

---

* units of measurements are total As (ug per 100 cm^2)

** estimate of standard deviation of As across test areas (see appendix, p. 11)

***estimate of standard deviation of measruement error (see appendix p. 11)

As Paired t-test of X_i

		Person A	Person Y	Paired difference D_i (Y-A)
Test Area	1	53.90	203.75	149.85
	2	105.77	313.75	207.98
	3	33.50	76.09	42.59
	4	68.38	71.42	3.04
	5	76.12	144.25	68.13
	6	51.09	52.00	0.91
	mean (X_i)	64.79	143.54	

mean (D_i) = 78.75
sd (D_i) = 83.65
n = 6

Paired t-test of the significance of the difference (143.54 - 64.79):

$t_5 = (78.75\sqrt{6})/83.63 = 2.31$

$p \approx 0.035$ 1-sided
$p \approx 0.070$ 2-sided

Sign test $p = (1/2)^6 = 1/64 = .016$ 1-sided
$p = 2 \times (1/2)^6 = 1/32 = .031$ 2-sided

II. ANALYSIS OF LN (As)

Ln (As) Analysis of Wipe Sampling

		Test Area 1	2	3	4	5	6
Person							
A	y_i	3.901	4.652	3.509	4.206	4.309	3.929
	d_i	.840	.273	.153	-0.395	.433	.190
Y	y_i	5.315	5.749	4.331	4.254	4.971	3.950
	d_i	.107	---	.102	-0.344	-0.026	.082

y_i = average ln (As) for ith test area: $(y_2 + y_1)/2$

d_i = difference between replicate ln (As) measurements $(y_2 - y_1)$ for ith test area

*This table is derived from the natural logarithms of the entries in the table entitled "Comparison of Wipe Sampling - Summary of Results"

ln (As) Summary Analysis*

	Person A	Person Y
mean (y_i)	4.08	4.76
sd (y_i)	.39	.70
n	6	6
mean (d_i)	0.25	-0.02
sd (d_i)	0.40	0.19
n	6	5

	Person A	Person Y
σ_t**	0.33	0.69
σ_e***	0.28	0.13

* units of measurements are ln (total As)
** estimate of standard deviation of ln (As) across test areas (see appendix, p. 11)
***estimate of standard deviation of measurements error (ln scale)

ln (As) Paired t-test of y_i

		Person A	Person Y	Paired difference D_i (Y-A)
	1	3.901	5.315	1.41
	2	4.652	5.749	1.10
Test Area	3	3.509	4.331	0.82
	4	4.206	4.254	0.05
	5	4.309	4.971	0.66
	6	3.929	3.950	0.02
mean (y_i)		4.08	4.76	

mean (D_i) = 0.68
sd (D_i) = 0.56
n = 6

Paired t-test of the significance of the difference (4.76 - 4.08):

$$t_5 = (0.68\sqrt{6})/0.56 = 2.97$$

$p \approx .017$ 1-sided
$p \approx .034$ 2-sided

Sign test $p = (1/2)^6 = 1/64 = .016$ 1-sided
$p = 2 \times (1/2)^6 = 1/32 = .031$ 2-sided

III. ALTERNATIVE ANALYSES OF AS AND LN (As) THAT EXCLUDE THE ABERRANT OBSERVATION 313.75 RECORDED FOR PERSON Y ON TEST AREA 2

One might question whether the observation 313.75 for Y on test area 2 distorts the analyses that are presented and summarized in this note. If this observation, which seems to be aberrant, is omitted from the analysis of As levels, one derives the results tabled below:

	Person A	Person Y
mean (X_i)	64.79	109.50
sd (X_i)	24.92	63.17
n	6	5
mean (d_i)	15.35	1.15
sd (d_i)	24.99	17.01
n	6	5
$\hat{a}_t$	21.56	62.59
$\hat{a}_e$	17.67	12.03

Paired t-test of (109.50 vs 64.79): $t_4 = 2.15$, $p = .102$ (two-sided). Sign test: $p = .062$ (two-sided)

This analysis may be compared with that reported on pages 4 and 5. Excluding the observation 313.75 reduces the estimate of the average As level recorded by Y and reduces the estimate of local area variation for Y.

If, analogously, the observation ln (313.75) = 4.79 is omitted from the analysis of ln (As), one derives the following results:

	Person A	Person Y
mean (y_i)	4.08	4.56
sd (y_i)	0.39	0.56
n	6	5
mean (d_i)	0.25	-0.02
sd (d_i)	0.40	0.19
n	6	5
r_t	0.33	0.55
r_e	0.28	0.13

Paired t-test of 4.08 vs 4.56: $t_4 = 2.24$, $p = .074$ (2-sided). Sign test: $p = .062$ (2-sided).

This analysis may be compared with that reported on pages 7 and 8. Excluding the observation 313.75 reduces the estimate of the average ln (As) level recorded by Y and reduces the estimate of test area variation for Y.

The preceding two analyses alter the quantitative results of the study data but do not materially alter their interpretation, which has been given on page 1.

Appendix

Estimates of Variability of Test Areas and Measurement Error

Technical Notes

Repeated Measures Model

$X_{ij} = u_A + T_i + e_{ij}$	jth replicate (j = 1,2) on ith test area (i = 1,2,...,6) for Person A.
$X_{ij} = u_Y + T_i + e_{ij}$	jth replicate on ith test area for Person Y.
$X_i = u + T_i + e_i$	Mean for ith test area, Where u denotes u_A or u_Y.
$d_i = e_{i2} - e_{i1}$	Replicate difference for ith test area

var $(X_i) = (\sigma_t)^2 + (\sigma_e^2)/2$, assuming X_i based on the average of two replicates. σ_t^2 denotes the variance of As across the test areas. (σ_e^2) denotes the error variance in measuring arsenic on a test area.

var $(d_i) = 2\,\sigma_e^2$

From the above, one finds that

1/2 var (d_i) estimates σ_e^2, and

var (X_i) - 1/4 var (d_i) estimates σ_t^2.

Note: var $(X_i) = [\text{sd } (X_i)]^2$, shown on pp. 4 & 7.

var $(d_i) = [\text{sd } (d_i)]^2$, shown on pp. 4 & 7.

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March 28, 2003

Office of the Secretary
Consumer Product Safety Commission
4330 East-West Highway
Room 502
Bethesda, MD 20814

Re: ACCA Ban Petition, Petition HP 01-3; 68 Fed. Reg. 7510 (February 14, 2003)

Dear Sir or Madam:

The American Forest & Paper Association ("AF&PA") supplements its March 18, 2003 oral testimony presented to the Consumer Products Safety Commission ("CPSC") with the following comments.

During the March 18 public meeting, Chairman Stratton asked the forest products industry panel (paraphrasing), "Why does it matter," if CPSC bans CCA for residential and recreational uses, "it's already off the market?"

It matters to the forest products industry for several reasons. First, principles of good government require that federal agencies act only when necessary and, then, only to the extent authorized by statute or required to fulfill the agency's statutory responsibility. As we pointed out in our testimony, and as the CPSC Staff Briefing Package acknowledges, CCA registrants have agreed to "terminate essentially all residential uses of CCA, including use in playground equipment, effective December 31, 2003." There is simply no need for CPSC to act on the ban petition, as the petitioners have already gotten the remedy they seek.

Moreover, the CCA registrants voluntarily agreed to terminate most residential uses of CCA to respond to market demand for wood preservatives that do not contain arsenic. They did not do so because such uses pose a risk to human health. In point of fact, EPA's Jack Housenger (Associate Director, Antimicrobials Division, Office of Pesticide Programs) reminded CPSC in his March 17, 2003 testimony that "it is important to note also that EPA has not concluded that CCA-treated wood poses unreasonable risks to the public for existing structures made with CCA-treated wood," echoing Administrator Whitman's similar statement when she announced the registrants voluntary action. CPSC cannot "piggy-back" a supposedly risk-based ban on a voluntary action, which responded, not to risk, but to market forces.

In addition, CPSC is constrained by statute to act only on complete, sound science. The record of the March 17-18 public meeting is replete with evidence showing that the science underlying the CPSC staff risk assessment is neither complete, nor sound. CPSC staff's risk conclusions differ from those of the U.S. Environmental Protections Agency and are not supported by the Florida Physicians

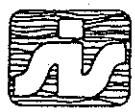
Arsenic Workgroup, appointed by Florida's Secretary of Health. Moreover, action now on CPSC staff's risk estimates would be premature, because it would not reflect the results of on-going risk assessment work by EPA, some of which is joint research with CPSC itself. EPA's Jack Housenger testified March 17 that EPA will soon complete three research projects—a surface residue bioavailability study, soil residue bioavailability study, and a hand wipe study. In addition, EPA and CPSC are engaged in joint research on the effectiveness of exposure mitigation measures. All of these studies bear substantially on how CPSC should address the ban petition. It simply makes no sense to act before they are completed later this year.

Finally, any CPSC action suggesting that CCA-treated wood poses risks to human health may affect adversely the market for continuing, industrial uses of CCA-treated wood and may even disrupt the market for wood treated with non-arsenic-based preservatives. CPSC should not, therefore, act lightly. It must understand the serious economic consequences of its pronouncements about products and be very careful to act only when necessary and when supported by sound science. Neither of those conditions is present in this proceeding.

In sum, "it matters" to the forest products industry. It matters that CPSC adhere to principles of good government, base its actions only on complete, sound science, and avoid possible disruption to a $8 billion industry when no action is warranted.

Respectfully submitted,

Sharon H. Kneiss
Vice President



S.I. Storey
LUMBER COMPANY, INC.

March 28, 2003

Consumer Product Safety Commission

RE: Petition HP 01-3

Thank you for the opportunity to submit additional comments regarding petition HP 01-3, a petition to ban CCA treated lumber in playground structures. These comments are in addition to those I offered during the oral argument phase on March 18, 2003.

The first of two additional points I would like to make are related to some of the oral arguments made before the commission. First, the Chairman asked our panel that if the issue is truly moot due to the re-registration process before the EPA and if that phase out has indeed accomplished the goal of the petition, then what is the harm in the CPSC granting the petition to ban? Several noted persons, including Dr. Louis Sullivan, appeared before you and pointed out that the Staff Report made some assumptions that at best overstated the exposure boundaries and perhaps were out right incorrect. Therefore, if the CPSC were to grant the ban based on the staff's findings and further study and research supports the scientists' argument about the incorrect assumptions in the report, then the reputation of the CPSC is at stake. The CPSC is charged with protecting the safety of the consumers and to grant a ban when there are questions about the data that the decision is based could only serve to impact a great organization" credibility. As a consumer and a citizen, that is not something I would like to see happen because I rely on the CPSC to protect my safety as well as that of my family and the public as it has done for many years.

The second point against the petition is another that Dr. Sullivan actually touched on during his presentation. Granting the petition would potentially cause undue and unfounded public alarm over numerous existing playgrounds and that public alarm is not warranted in my opinion and in the opinion of those that made presentations to you. The danger of this alarm would be, in trying to protect the safety fo the consumers' children, the CPSC would potentially be causing greater harm because the net effect would be in all likelihood be less physical activity by our young people. The Centers for Disease Control has found that Type 2 diabetes, long thought to be adult onset, is increasing at an alarming and dangerous rate among our young people. Much of this is attributed to their lifestyle and their decrease in physical activity replaced with an increase in video games, computers and television use. The lack of exercise is impacting our nation's young people negatively. Therefore, any action by the CPSC not based on 100% sound science that has the potential to lessen physical activity among our young people could in fact cause greater harm. Indeed, I believe our electronic age is more harmful to our young than any treated wood play structure is or has been.

Therefore, I once again urge the Commission to either (1) deny the petition outright recognizing the potential for incomplete science and assumptions in the staff report and no proof of increased risk or (2) defer any action on the petition as the commission's own staff has recommended.

I thank you again for the opportunity to present to you for your thoughtful consideration.

Sincerely,

Hal M. Storey

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March 28, 2003

Office of the Secretary
Consumer Product Safety Commission
4330 East-West Highway
Room 502
Bethesda, MD 20814

Re: ACCA Ban Petition, Petition HP 01-3; 68 Fed. Reg. 7510 (February 14, 2003)

Dear Sir or Madam:

The Southern Pine Council (SPC) supplements its March 18, 2003 oral testimony presented to the Consumer Products Safety Commission (CPS") with the following comment.

The petitioners raised concerns over CCA-treated remaining in the residential supply chain for "years" after the December 31, 2003 deadline for ceasing manufacture of the product. This simply is not a feasible scenario. The inventory carrying costs for treated wood are such that stockpiling significant supplies (i.e. years' worth of product) is not a financially viable proposition. Treated wood bound for the retail market is stored under cover to maintain a clean, bright, "new" appearance and both manufacturers and retailers are limited in terms of shed space on how much product they can hold in inventory. At most, CCA-treated product could be expected to linger in the residential supply chain for weeks or possibly months, but certainly not years.

Thank you for the opportunity to address the Commission.

Respectfully submitted,

Debbie Burns
Vice President – Public Affairs

Stevenson, Todd A.

From: Debbie Burns [debbie@slma.org]
Sent: Friday, March 28, 2003 4:34 PM
To: Stevenson, Todd A.; Hammond, Rocky
Subject: ACCA Ban Petition, Petition HP 01-3

CPSC testimony for Burns.doc

RE: ACCA Ban Petition, Petition HP 01-3
Supplemental comments to my oral testimony at the March 17 CPSC hearing are attached.

Debbie Burns
Vice President - Public Affairs
Southeastern Lumber Manufacturers Association
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404-361-1445

Comments on CPSC's analysis of cancer risk to children from contact with CCA-treated wood products

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Prepared and submitted at the request of
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About the author. Ph.D. in statistics from Johns Hopkins University. Numerous publications on statistics and applications to risk assessment. With regard to arsenic, served on committees (NRC/NAS subcommittee on arsenic in drinking water, Arsenic Task Force of the Society for Environmental Geochemistry and Health), workshops on research needs (NCI/NIEHS/EPA, American Water Works Association), drafted the position paper of the American Council on Science and Health, presented invited and contributed papers at numerous conferences, co-authored 12 articles - 5 in conference proceedings, 7 in refereed journals (2 invited). Research supported by U.S. EPA, industry, and trade associations (e.g., American Water Works Association).

Introduction. The CPSC claims that it has dealt with sources of uncertainty and variability, but that is not quite accurate. They have considered a range of values for some of their parameters (such as concentration of arsenic on children's hands, hand-to-mouth transfer, exposure frequency, and bioavailability), which is commendable, but they have not considered the uncertainty in their methodology or the risk estimates of cancer from arsenic in drinking water taken from the NRC (National Research Council) and EPA (U. S. Environmental Protection Agency) reports. "Uncertainty refers to lack of knowledge in the underlying science" (NRC1, p.109), and uncertainties require assumptions, either implicitly or explicitly, to derive numerical values of risk. The credibility of the assumptions affects the extent to which the CPSC claim of excess lifetime risk of lung and bladder cancer of 2-100 per million for children who play on CCA-treated playground structures is warranted (or to what is referred to as "an approximation of reasonable 'worst' and 'best' cases", ranging from 0.2 per million to 5,000 per million across their range of parameters, is warranted).

Two critical assumptions are discussed below, the first related to CPSC's technical approach and the second related to the Taiwan data used in the NRC and EPA risk assessments for arsenic in

drinking water. In the first case, the assumption is due to insufficient information about the mode-of-action of arsenic carcinogenicity, a biological consideration. In the second case, the assumption is because the exposure data in the principal study used for risk assessment of arsenic in drinking water is highly aggregated, instead of specific to individuals, a statistical consideration (technically refered to as ecological exposure data, and thus making statistical inference subject to what epidemiologists refer to as the "ecological fallacy"). Both assumptions are the result of genuine limitations of the science, or the available data, and both are important to warranting CPSC's estimates of the cancer risk.

The premise in the discussion that follows is that conclusions from risk analysis for health effects should be as strong as warranted, but not stronger. Just how strong is warranted depends on statistical characteristics, such as the quality and level of detail of the available data and the appropriateness of the statistical methodology, and on consistency of the data analysis with biological expectations. In short, claims based on data analysis for health effects are warranted by both statistical and biological considerations.

Assumption 1. Excess cancer risk from arsenic ingested from CCA-wood products at 2-6 years of age years is the same as if that total arsenic intake were distributed evenly over a lifetime.

The CPSC analysis begins with the lifetime risk estimates of bladder and lung cancer from the NRC and EPA. Both were determined from the same data in southwestern Taiwan, which is discussed next, and the comments of this section apply equally to either the NRC or EPA data. The CPSC calculated a LADD (lifetime average daily dose) that it multiples by a cancer potency factor (Q), where Q is described as the "[lifetime] cancer risk per unit of daily [arsenic] exposure" (CPSC, p.306). CPSC staff calculated a value for Q of 0.023 $(\mu g/kg/day)^{-1}$ (CPSC, p. 22) from the NRC analysis and a range of about 0.00041 to 0.0037 $(\mu g/kg/day)^{-1}$ (CPSC, p.22) from the EPA analysis. The lifetime daily dose is the estimated daily intake if the total arsenic consumed by a child from contact with CCA-wood products during the ages of 2-6 inclusive were spread evenly over a lifetime of average duration. That implies that lifetime risk (1) increases linearly with duration (number of days or years) of exposure, and (2) is determined by

cumulative arsenic intake without regard to exposure regimen, such as the ages at which exposure begins and terminates, and whether exposure is continuous or intermittent.

With regard to (1), NRC2 statistical models for cancer risk from lifetime exposure (NRC2, Table 5.4), all include the effect of duration (the same as age in those data) as quadratic rather than linear, i.e., the effect of duration of exposure increases disproportionately to dose. This suggests that the CPSC formula probably produces estimates that are too high. The formula is being used an approximation to the NRC2 model that was chosen (or the EPA model in the case of the EPA estimates). The formula could be checked by calculating lifetime cancer risks for an array of exposure levels (units of arsenic per day) and exposure durations (number of years) and the values compared with the outcomes that would be obtained using the NRC and EPA models from which the values of Q were determined. That could not be done for this review because more technical detail is needed than has been published in the relevant reports. If the CPSC formula is not a good approximation for continuous lifetime exposure, then it could not be expected to apply to partial lifetime exposure as experienced by children exposed to CCA.

With regard to (2), cancer risk from arsenic exposure for a limited time-period, e.g., five years, can depend on factors such as the age exposure begins, the time since exposure ended, and whether exposure was intermittent or continuous, all of which are related to the biology of the relevant cancer mechanism(s). The issue of intermittent versus continuous exposure is related to whether periods of no exposure provide some opportunity for recovery/regeneration from the effects of exposure. Other factors of interest are whether arsenic is a complete or incomplete carcinogen, whether late or early stages, or both, of cancer development are affected, etc. Unfortunately, research on the mechanism(s) of arsenic carcinogenicity has been hampered somewhat by the difficulty of inducing cancer in experimental animals from exposure to arsenic.

There are few substances with an enough epidemiological data to address such issues of partial lifetime exposure, although tobacco smoking is an exception. Tobacco smoke is known to contain a large number of human carcinogens, so its biological mechanisms are probably a mix of possibilities. The risk of lung cancer appears to be higher for people who started smoking at a

younger age, but risk decreases with time since smoking cessation, which has been interpreted as suggesting both initiation and promotion capabilities of tobacco smoke components (U.S. EPA, 1992, Sec. 4.2.2). One cannot draw conclusions about arsenic based on the example of tobacco smoke, but it demonstrates the importance of maintaining a biological perspective.

Conclusion 1. The CPSC accepts the results of NRC2 but its approach to modify risk estimates to apply to arsenic intake from CCA is inconsistent with the NRC2 analysis. If one accepts the NRC2 cancer risk estimates (to be discussed next), then CPSC probably overestimates risk from CCA. Implicit biological assumptions are introduced about the mechanism(s) of arsenic carcinogenicity that may not apply. CPSC's claim of excess cancer risk, and the numerical estimates, from CCA-treated wood are unwarranted on either statistical or biological grounds.

Assumption 2. The risk analyses of cancer from arsenic in drinking water based on the southwestern Taiwan data assume that all persons from the same village in the southwestern Taiwan study area were exposed to the same arsenic concentration in drinking water, namely the median value of the wells tested in the village.

The two NRC reports mention several sources of uncertainty, but only one, the potential for misclassification of human exposure to arsenic in the data from southwestern Taiwan, is discussed here. By way of background, the exposure data consists of well tests for arsenic in villages made prior to about 1970, while the data for bladder and lung cancer were taken from mortality records for the period 1973-1986 that included the cause of death and the village of residence. Thus, individual mortality records for bladder cancer deaths connect an individual to a village, but not to a specific well(s) within the village. The assumption made in the NRC reports is that persons from the same village were exposed to the same level of arsenic concentration in drinking water, specifically the median value of the wells tested within the village. Wells within the same village, however, often differed markedly in arsenic concentrations. Figure 1, showing the arsenic concentrations by village, for villages with more than one well, was constructed from Table A10-1 of NRC1. The same data were analyzed more fully by Morales et al. (2000), that was cited heavily in NRC2 and in the EPA report.

The first village listed in Figure 1, O-G, had a relatively large number of cancer occurrences. There were five wells with arsenic concentration test results of 10, 10, 30, 259, and 770 μg/L. There was a total of 10,000 person-years for the village with 11 bladder or lung cancer deaths. The analyses of the two NRC reports, and EPA, treat the village the same as if there were one well with arsenic concentration of 30 μg/L, effectively assuming that all 11 cancer deaths occurred at an arsenic concentration of 30 μg/L. The range of well tests is not so extreme across all villages, but it is readily apparent from the figure that the example just described is not an isolated case. The potential for serious exposure misclassification is obviously high. The data contain only one well test for 20 of the 42 villages. The effect of such data on risk estimation is apparent in a diagram in which different dose-response models were fit to the data. First, however, it maybe useful to see an example of a model fit to good dose-response data.

The data in Figure 2 are from mortality of rats exposed to hydrogen sulfide, and are used here strictly for illustration, with a logistic model fit to the data. A statistical measure of the goodness of fit, or something such as the AIC (Akaike Information Criteria) used by the NRC to compare different alternatives, is not adequate by itself; it is necessary to graphically examine the fit of the data. In this case, it is apparent graphically that the model describes the data well – the data are close to the curve and predicted values calculated from the curve should be reasonable. Another model might fit the data about equally well, but to do so it is clear that it would have to be very close to the current curve. Thus one can have some level of comfort in using the fitted curve to estimate risk at arbitrary exposure values that may not have been actually observed.

By contrast, several different models were statistically fit to the Taiwan data, with disagreement between EPA's Science Advisory Board and the NRC2 subcommittee on whether the dose-response analysis should include no external comparison group, or a comparison group consisting of either a southwestern region of Taiwan or all of Taiwan (NRC2, Ch. 5). The results for the three alternatives, and selected model choices, are displayed in Figure 3, which appeared in Morales et al. (2000) and NRC2 (Lifetime risk of death from bladder cancer for males plotted against U.S. equivalent arsenic concentration in μg/L of drinking water). It is clear that the data

are so variable that none of the models provide a good fit to the data. One point near the center of the exposure range is exceedingly high, suggesting that it might be an outlier. More than one model has about the same AIC value, indicating that they cannot be distinguished on a statistical measure of fit (the AIC provides a relative comparison of fits – no statistical measure of fit was found). As one can see graphically, the estimated risks very close to the origin vary widely for different models, so there is considerable model sensitivity (as noted in NRC2 and Morales et al.). Nevertheless, NRC2 settled on one of the models linear in dose, using the southwestern Taiwanese region as the comparison group, and concluded that it is a "biologically plausible model that provides a satisfactory fit to the epidemiological data and represents a reasonable model choice for use in arsenic risk assessment" (NRC2, Ch. 5, Summary).

In light of Figure 3, it is hard to see how that statement could be justified even if the data were valid and reliable. Considering the high exposure misclassification expected from treating individuals within a village as all drinking water with the same arsenic concentration (the median-concentration well in the village), there would be little basis for much credence in any model fit to the data (Figure 1). The validity and reliability of the data and the appropriateness of the statistical model are both questionable. Regarding biological plausibility, NRC1 (Ch. 7.) notes that the mode-of-action of carcinogenicity has not been established, and that it is prudent not to rule out the possibility of a linear response. However, it also states that the several modes-of-action that are considered plausible (namely, indirect mechanisms of mutagenicity) would lead to a sublinear dose-response curve at some point below the point at which a significant increase in tumors is observed (i.e., less than linear response at sufficiently low arsenic concentrations). Thus, the NRC2 model choice with linear dose is not the most biologically plausible option, nor does it appear to be among those with superior statistical fit. According to NRC2 (Ch. 5), "statistically superior fits were produced using models that included a log or square-root transformation of dose (Morales, 2000), despite the fact that those models are not as biologically plausible as other ones." When the biological information and the statistical outcomes collide, something is fundamentally wrong, and in this case one can find "probable cause" in the misclassification of study subjects to arsenic.

Conclusion 2. The NRC2 claim that chronic exposure to arsenic causes cancer is supported, but conclusions regarding the magnitude of risk at specific exposure levels, based on statistical modeling of the southwestern Taiwan data, are beyond the level of detail warranted by the data. Furthermore, the statistical analysis is not consistent with the most biologically plausible mode-of-action(s) of arsenic carcinogenicity

Summary Conclusion. Of the two sources of uncertainty described above, the first addressed an assumption that CPSC made to extrapolate cancer risk estimates based on chronic exposure to intermittent childhood exposure from contact with CCA-treated wood products, given that the NRC2 estimates for chronic exposure to low arsenic concentrations in drinking water are valid and reliable. The second source of uncertainty questioned the validity and reliability of the NRC2 estimates of risk. It is clear from the data of southwestern Taiwan and elsewhere that lifetime exposure to arsenic concentrations in drinking water of several hundred μg/L produces detrimental health effects, including cancer of the bladder and other organs. Claims that these detrimental effects also occur at small arsenic intakes, e.g., 10μ/L (10-20 μg/day), and that quantitative estimates of risk determined from the available data are valid and reliable, is more speculation than science. The implications for the CPSC analysis is that they are trying to ferret out cancer risks at extremely small arsenic intakes for which it is not at all clear that there even is a cancer risk.

Addendum: Are the NRC1, Morales et al., and NRC2 concerned about the southwest Taiwan database?

This is not a full and complete discussion, which would be much too lengthy, and one could argue against quoting text from these sources out of context. It describes the impression of the current author, with some supporting quotations.

NRC1 sends a mixed message. It seems to be concerned about the quality of the southwestern Taiwan data, but draws some rather strong conclusions anyway. Within the body of the report, NRC1 provides some instruction on dose-response analysis and an analysis of the bladder cancer data with the proviso that "it is important to emphasize again that the results are not to be

interpreted as a formal risk assessment, or as an endorsement of these data for the use of risk assessment" (NRC1, p. 273). This is consistent with the preface that states "EPA did not request, nor did the subcommittee endeavor to provide, a formal risk assessment for arsenic in drinking water" (NRC1, p. 2), and the recommendation that "Additional epidemiological evaluations are needed to characterize the dose-response relationship for arsenic-associated cancer and non-cancer endpoints, especially at low doses. *Such studies are of critical importance for improving the scientific validity of risk assessment* [emphasis added] (NRC1, p.3).

The executive summary of NRC1, however, then proceeds with risk assessment estimates, specifically a bladder-cancer risk of 1 to 1.5 per 1,000, with speculation that the combined risk with lung cancer included could be on the order of 1 per 100, and concludes that EPA's MCL for arsenic of 50 μg/L requires downward revision as promptly as possible. Those are pretty strong conclusions based on data explicitly stated as not being endorsed for the use of risk assessment. The lung cancer data from the Taiwan data had not been analyzed at all, and the risk from lung cancer was based on the claim that "some studies have shown that excess lung cancer deaths attributed to arsenic are 2-5 fold greater than the excess bladder cancer deaths" (NRC1, p.8). The supporting statement in the body of the report appears to be that studies in Chile (Smith et al., 1998) and Argentina (Hopenhayn-Rich et al., 1996, 1998) "observed risks of lung and bladder cancer of the same magnitude as those reported in the studies in Taiwan at comparable levels of exposure" (NC1, p.292). The current author is not aware of any analyses to support that statement, however, and in the opinion of the second NRC committee, exposure levels were not sufficiently well quantified in those studies to support a quantitative dose-response analysis (NRC2, Ch. 5).

The article by Morales et al. (2000), that analyzed the southwestern Taiwan data in considerable detail, employing a number of different models and addressing cancer risk of bladder, lung, and liver, appeared after NRC1 and was influential to the subsequent EPA analysis and to NRC2. The article expresses concerns about the Taiwan data but, like NRC1, doesn't let it interfere with drawing some substantive conclusions about the risk of arsenic. Results were reported to depend highly on the choice of model, as well as whether or not a comparison population was used in the